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Glut-1 as a receptor for HTLV envelopes and its uses

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GLUT-1 AS A RECEPTOR FOR HTLV ENVELOPES AND ITS USES

The invention relates to the use of the ubiquitous vertebrate glucose transporter GLUT1 represented by SEQ ID NO : 2, or of fragments or sequences derived thereof, for the *in vitro* diagnosis of cancers, when used as a tumor marker, or for the screening of compounds useful for the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV, or pathologies linked to an overexpression of GLUT1 on cell surfaces, or the *in vitro* detection of GLUT1 on cell surfaces. The invention also relates to pharmaceutical compositions containing GLUT1, or fragments or sequences derived thereof, and their uses such as in the frame of the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV.

The human T-cell leukemia virus (HTLV) is associated with leukemia and neurological syndromes. The role of viral envelopes in HTLV physiopathology is unclear and the envelope receptor, found in all vertebrate cell lines, remains unidentified.

HTLV envelope glycoproteins induce syncytium formation in vitro but their physiopathological effects are unclear. All vertebrate cell lines express functional HTLV envelope receptors, including cells resistant to HTLV envelope-mediated syncytium formation. We found that expression of the HTLV receptor-binding domain decreased lactate production due to diminished glucose consumption whereas binding-defective envelope mutants did not alter glucose metabolism. Glucose starvation increased HTLV receptor expression, reminiscent of nutrient sensing responses. Accordingly, overexpression of GLUT-1, the ubiquitous vertebrate glucose transporter, specifically increased HTLV envelope binding and GLUT-1 colocalized with HTLV envelopes. Moreover, HTLV envelope binding was highest in human erythrocytes, where GLUT-1 is abundantly expressed and is the sole glucose transporter isoform. These results demonstrate that GLUT-1 is an HTLV envelope receptor, and that this ligand/receptor interaction likely participates in the immunological and neurological disorders associated with HTLV infection.

Thus, the invention relates to the use of the ubiquitous vertebrate glucose transporter GLUT1 represented by SEQ ID NO : 2, or of fragments or sequences derived thereof, said fragments or derived sequences being able to bind to the envelope proteins of the primate T-cell leukemia viruses (PTLV), or of cells expressing GLUT1, for:

- the screening of compounds useful for :

* the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV,

* the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces,

* the *in vitro* detection of GLUT1 on cell surfaces,

said compounds being selected for their ability to bind specifically to said GLUT1,

- the detection, concentration, and/or purification of PTLV or variants thereof, or of PTLV envelope proteins, or fragments thereof,

- the preparation of drugs for the prevention or the treatment of pathologies either linked to an infection of an individual or an animal with a PTLV, such as HTLV-1, HTLV-2, STLV-1, STLV-2, STLV-3, or their variants, or linked to the presence of PTLV SU-related sequences in such individuals or animals,

- the *in vitro* diagnosis of cancers, when used as a tumor marker.

For illustration purpose, screened compounds mentioned above can be selected for their ability to bind specifically to said GLUT1 according to the following method using a EGFP-tagged GLUT1-binding component derived from PTLV RBD (receptor binding domain) as an example of such compound able to bind to GLUT1.

A EGFP-tagged Glut1-binding component derived from PTLV RBD is applied onto live or fixed suspension or attached cells. After washes with appropriate buffer, cells are incubated for 30 min at RT, washed and analyzed or quantified as attached on an appropriate support on a fluorescent microscope or as individual cell suspension on a fluorescent analysis ell sorter (FACS). Alternatively, a non-fluorescent GLUT1-binding component derived from PTLV RBD is applied as described above and revealed with a secondary fluorochrome-tagged reagent such as a fluorochrome-tagged secondary antibody directed against the PTLV RBD or against a non fluorochrome tag attached to the said PTLV RBD component.

The invention relates more particularly to the use as defined above, of fragments of GLUT1 chosen among the followings :

- SEQ ID NO : 25 : NAPQKVIEEFY
- SEQ ID NO : 26 : NQTWVHRYGESILPTTLTTLWS
- SEQ ID NO : 27 : KSFEMLILGR
- SEQ ID NO : 28 : DSIMGNKDL
- SEQ ID NO : 29 : YSTSIFEKAGVQQP
- SEQ ID NO : 30 : EQLPWMSYLS
- SEQ ID NO : 31 : QYVEQLC

These fragments of GLUT1 correspond to the predicted extracellular loops of human GLUT1 as described by Mueckler, M., and C. Makepeace. 1997. Identification of an amino acid residue that lies between the exofacial vestibule and exofacial substrate-binding site of the GLUT1 sugar permeation pathway. J Biol Chem. 272(48):30141-6.

The invention also concerns the use of compounds selected for their ability to bind specifically to GLUT1 as defined above, for the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV, such as pathologies corresponding to adult T cell leukemia (ATL), HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP), as well as other HTLV-associated syndromes such as large granular lymphocyte (LGL) leukaemia (Loughran, T. P., K. G. Hadlock, R. Perzova, T. C. Gentile, Q. Yang, S. K. Foung, and B. J. Poiesz. 1998. Epitope mapping of HTLV envelope seroreactivity in LGL leukaemia. Br J Haematol. 101(2):318-24.), uveitis (Mochizuki, M., A. Ono, E. Ikeda, N. Hikita, T. Watanabe, K. Yamaguchi, K. Sagawa, and K. Ito. 1996. HTLV-I uveitis. J Acquir Immune Defic Syndr Hum Retrovirol. 13 Suppl 1:S50-6.), infective dermatitis (La Grenade, L., R. A. Schwartz, and C. K. Janniger. 1996. Childhood dermatitis in the tropics: with special emphasis on infective dermatitis, a marker for infection with human T-cell leukemia virus-I. Cutis. 58(2):115-8.), arthropathies (Nishioka, K., T. Sumida, and T. Hasunuma. 1996. Human T lymphotropic virus type I in arthropathy and autoimmune disorders. Arthritis Rheum. 39(8):1410-8.), cutaneous T cell lymphoma (mycosis fungoides) (1.Hall, W. W., C. R. Liu, O. Schneewind, H. Takahashi, M. H. Kaplan, G. Roupe, and A. Vahlne. 1991. Deleted HTLV-I provirus in blood and cutaneous lesions of patients with mycosis fungoides. Science. 253(5017):317-20. 2. Zucker-Franklin, D., B. A. Pancake, M. Marmor, and P. M. Legler. 1997. Reexamination of human T cell lymphotropic virus (HTLV-I/II) prevalence. Proc Natl Acad Sci U S A. 94(12):6403-7), polymyositis (Saito M, Higuchi I, Saito A, Izumo S, Usuku K, Bangham CR, Osame M. Molecular analysis of T cell clonotypes in muscle-infiltrating lymphocytes from patients with human T lymphotropic virus type 1 polymyositis. J Infect Dis. 2002 Nov 1;186(9):1231-41), and potentially other idiopathic diseases in which PTLV or PTLV sequences may be involved.

The invention relates more particularly to the use for the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV, of compounds chosen among the followings :

- androgenic steroids (36: May JM, Danzo BJ. Photolabeling of the human erythrocyte glucose carrier with androgenic steroids. Biochim Biophys Acta. 1988 Aug 18;943(2):199-210),

- cytochalasin B, forskolin, dipyridamole, isobutylmethylxanthine (20: Hellwig B, Joost HG. Differentiation of erythrocyte-(GLUT1), liver-(GLUT2), and adipocyte-type (GLUT4) glucose transporters by binding of the inhibitory ligands cytochalasin B, forskolin, dipyridamole, and isobutylmethylxanthine. Mol Pharmacol. 1991 Sep;40(3):383-9),

- ethanol (Krauss SW, Diamond I, Gordon AS. Selective inhibition by ethanol of the type 1 facilitative glucose transporter (GLUT1). Mol Pharmacol. 1994 Jun;45(6):1281-6),

- genistein (Vera JC, Reyes AM, Carcamo JG, Velasquez FV, Rivas CI, Zhang RH, Strobel P, Iribarren R, Scher HI, Slebe JC, et al. Genistein is a natural inhibitor of hexose and dehydroascorbic acid transport through the glucose transporter, GLUT1. J Biol Chem. 1996 Apr 12;271(15):8719-24),

- cadmium (Lachaal M, Liu H, Kim S, Spangler RA, Jung CY. Cadmium increases GLUT1 substrate binding affinity in vitro while reducing its cytochalasin B binding affinity. Biochemistry. 1996 Nov 26;35 (47):14958-62),

- barbiturate (el-Barbary A, Fenstermacher JD, Haspel HC. Barbiturate inhibition of GLUT-1 mediated hexose transport in human erythrocytes exhibits substrate dependence for equilibrium exchange but not unidirectional sugar flux. Biochemistry. 1996 Dec 3;35(48):15222-7),

- dehydroascorbic acid (Rumsey SC, Kwon O, Xu GW, Burant CF, Simpson I, Levine M. Glucose transporter isoforms GLUT1 and GLUT3 transport dehydroascorbic acid. J Biol Chem. 1997 Jul 25;272(30):18982-9),

- tricyclic antidepressants (Pinkofsky HB, Dwyer DS, Bradley RJ. The inhibition of GLUT1 glucose transport and cytochalasin B binding activity by tricyclic antidepressants. Life Sci. 2000;66(3):271-8.),

- oestradiol, genistein and the anti-oestrogens, faslodex (ICI 182780), tamoxifen (Afzal I, Cunningham P, Naftalin RJ. Interactions of ATP, oestradiol, genistein and the anti-oestrogens, faslodex (ICI 182780) and tamoxifen, with the human erythrocyte glucose transporter, GLUT1. Biochem J. 2002 Aug 1;365(Pt 3):707-19),

- gamma agonists of peroxisome proliferator-activated receptors (PPAR) such as thiazolidinedione (troglitazone, pioglitazone, ro siglitazone) ("TZDs modify astrocyte metabolism and mitochondrial function, which could be beneficial in neurological conditions where glucose availability is reduced" from Dello Russo C, Gavrilyuk V, Weinberg G,

Almeida A, Bolanos JP, Palmer J, Pelligrino D, Galea E, Feinstein DL.. Peroxisome proliferator-activated receptor gamma thiazolidinedione agonists increase glucose metabolism in astrocytes. J Biol Chem. 2003 Feb 21;278(8):5828-36).

The invention also relates to the use of compounds selected for their ability to bind specifically to GLUT1 as defined above, for the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces, such as :

- cancers, such as :

. squamous cell carcinoma (Kunkel M, Reichert TE, Benz P, Lehr HA, Jeong JH, Wieand S, Bartenstein P, Wagner W, Whiteside TL. Cancer. 2003 Feb 15;97(4):1015-24),

. hypopharyngeal carcinoma (Mineta H, Miura K, Takebayashi S, Misawa K, Araki K, Misawa Y, Ueda Y. Anticancer Res. 2002 Nov-Dec;22(6B):3489-94),

. breast cancer (Brown RS, Wahl RL.Overexpression of Glut-1 glucose transporter in human breast cancer. An immunohistochemical study. Cancer. 1993 Nov 15;72(10):2979-85),

. cervical carinoma (Mendez LE, Manci N, Cantuaria G, Gomez-Marin O, Penalver M, Braunschweiger P, Nadji M. Expression of glucose transporter-1 in cervical cancer and its precursors. Gynecol Oncol. 2002 Aug;86(2):138-43),

. ovarian carcinoma (Cantuaria G, Fagotti A, Ferrandina G, Magalhaes A, Nadji M, Angioli R, Penalver M, Mancuso S, Scambia G.GLUT-1 expression in ovarian carcinoma: association with survival and response to chemotherapy. Cancer. 2001 Sep 1;92(5):1144-50),

. lung cancer (Ito T, Noguchi Y, Satoh S, Hayashi H, Inayama Y, Kitamura H. Expression of facilitative glucose transporter isoforms in lung carcinomas: its relation to histologic type, differentiation grade, and tumor stage. Mod Pathol. 1998 May;11(5):437-43. Younes M, Brown RW, Stephenson M, Gondo M, Cagle PT. Overexpression of Glut1 and Glut3 in stage I nonsmall cell lung carcinoma is associated with poor survival. Cancer. 1997 Sep 15;80(6):1046-51),

. pancreatic cancer (Reske SN, Grillenberger KG, Glatting G, Port M, Hildebrandt M, Gansauge F, Beger HG. Overexpression of glucose transporter 1 and increased FDG uptake in pancreatic carcinoma. J Nucl Med. 1997 Sep;38(9):1344-8),

. insulinoma (1: Boden G, Murer E, Mozzoli M. Glucose transporter proteins in human insulinoma. Ann Intern Med. 1994 Jul 15;121(2):109-12,

- inflammatory conditions,

- immune or auto-immune diseases, such as :

. autoimmune myocarditis (Tokita N, Hasegawa S, Tsujimura E, Yutani K, Izumi T, Nishimura T. Serial changes in 14C-deoxyglucose and 201Tl uptake in autoimmune myocarditis in rats. J Nucl Med. 2001 Feb;42(2):285-91),,

. in the frame of CD28 T-cell activation (Frauwirth KA, Riley JL, Harris MH, Parry RV, Rathmell JC, Plas DR, Elstrom RL, June CH, Thompson CB. The CD28 signaling pathway regulates glucose metabolism. Immunity. 2002 Jun;16(6):769-77),

. in the frame of immunomodulation (Moriguchi S, Kato M, Sakai K, Yamamoto S, Shimizu E. Decreased mitogen response of splenic lymphocytes in obese Zucker rats is associated with the decreased expression of glucose transporter 1 (GLUT-1). Am J Clin Nutr. 1998 Jun;67(6):1124-9),

- disorders of the central nervous system, such as facilitated glucose transporter protein type 1 (GLUT1) deficiency syndrome (review in Klepper J, Voit T. Eur J Pediatr. 2002 Jun;161(6):295-304.)

The invention relates more particularly to the use for the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces, of compounds chosen among the followings :

- polypeptides compounds corresponding to the envelope proteins of PTLV, or fragments or sequences derived thereof, said fragments or derived sequences being able to bind to GLUT1,

- glucose or derivatives such as galactose, 2-fluorodeoxyglucose, 2-deoxyglucose, 3-O-methylglucose

- androgenic steroids, cytochalasin B, forskolin, dipyridamole, isobutylmethylxanthine, ethanol, genistein, cadmium, barbiturate, dehydroascorbic acid, tricyclic antidepressants, oestradiol, anti-oestrogens, faslodex (ICI 182780), tamoxifen, gamma agonists of peroxisome proliferator-activated receptors (PPAR) such as thiazolidinedione, troglitazone, pioglitazone, ro siglitazone, as mentioned above.

The invention concerns more particularly the use for the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces, of polypeptides compounds chosen among the followings :

- the envelope protein of HTLV-1 corresponding to SEQ ID NO : 4, or of HTLV-2 corresponding to SEQ ID NO : 6, or of STLV-1 corresponding to SEQ ID NO : 8, or of STLV-2 corresponding to SEQ ID NO : 10, or of STLV-3 corresponding to SEQ ID NO : 12,

- fragments of the envelope proteins of PTLV, said fragments corresponding to polypeptides delimited in their N-terminal extremity by the amino acid located in position 1 to

90, or in position 75 to 90, and in their C-terminal extremity by the amino acid located in position 135 to 245, or in position 135 to 150, of said envelope proteins of PTLV, such as SEQ ID NO : 4, 6, 8, 10, 12,

- fragments of the envelope proteins of PTLV, said fragments corresponding to the following polypeptides :

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 83 to 89, and in its C-terminal extremity by the amino acid located in position 139 to 145, of the envelope protein of the strain MT-2 of HTLV-1 corresponding to SEQ ID NO : 4,

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 79 to 85, and in its C-terminal extremity by the amino acid located in position 135 to 141, of the envelope protein of the strain NRA of HTLV-2 corresponding to SEQ ID NO : 6,

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 83 to 89, and in its C-terminal extremity by the amino acid located in position 139 to 145, of the envelope protein of STLV-1 corresponding to SEQ ID NO : 8,

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 79 to 85, and in its C-terminal extremity by the amino acid located in position 135 to 141, of the envelope protein of STLV-2 corresponding to SEQ ID NO : 10,

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 82 to 88, and in its C-terminal extremity by the amino acid located in position 138 to 144, of the envelope protein of STLV-3 corresponding to SEQ ID NO : 12,

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 14,

I K K P N P N G G G Y Y L A S Y S D
P C S L K C P Y L G C Q S W T C P Y
T G A V S S P Y W K F Q Q D V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 16,

V K K P N R N G G G Y Y L A S Y S D
P C S L K C P Y L G C Q S W T C P Y
T G A V S S P Y W K F Q Q D V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 18,

I K K P N R N G G G Y Y L A S Y S D
P C S L K C P Y L G C Q S W T C P Y
T G A V S S P Y W K F Q Q D V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 20,

I K K P N R N G G G Y Y L A S Y S D
P C S L K C P Y L G C Q S W T C P Y
T G P V S S P Y W K F Q Q D V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 22,

I K K P N R N G G G Y H S A S Y S D P
C S L K C P Y L G C Q S W T C P Y A G
A V S S P Y W K F Q Q D V N F T Q E V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-2, said polypeptide having the following sequence SEQ ID NO : 24,

I R K P N R Q G L G Y Y S P S Y N D
P C S L Q C P Y L G S Q S W T C P Y
T A P V S T P S W N F H S D V

The invention relates more particularly to the use of compounds selected for their ability to bind specifically to GLUT1 as defined above, for the *in vitro* detection of GLUT1 on cell surfaces in the frame of processes for the *in vitro* diagnosis of cancers, said processes comprising the following steps :

- contacting a biological sample (such as tumor biopsies or cells or tissue manifesting or with a suspected aberrant GLUT1 expression profile) from an individual with a compound as defined above, said compound being optionally labeled, or susceptible to be recognized by a labeled molecule,

- determining the level of said compound bound to the cells contained in the biological sample and comparison with the level of binding of said compound to cells contained in the biological sample from an healthy individual.

The invention concerns more particularly the use of compounds as defined above for the *in vitro* diagnosis of cancers, characterized in that the compounds used are chosen among the compounds defined above selected for their ability to bind specifically to GLUT1.

The invention relates more particularly to the use of polypeptide compounds chosen among those defined above, or of nucleotide sequences encoding said polypeptides, for the preparation of vectors containing at their surface said polypeptides, said vectors being useful for targeting GLUT1 overexpressing cells in pathologies linked to an overexpression of GLUT1 on cell surfaces such as defined above, and more particularly tumor cells, or cells involved in the inflammatory mechanism, or activated cells of the immune system, or cells of

the central nervous system, said vectors containing molecules active against said pathologies, like antitumor molecules, or containing genes in the frame of gene therapy.

The invention also relates to the use of nucleotide sequences encoding polypeptides compounds selected for their ability to bind specifically to GLUT1 as defined above, such as nucleotide sequences encoding the polypeptides defined above, or fragments thereof, for the preparation, by substitution of one or several nucleotides of said nucleotide sequences, of mutant nucleotide sequences encoding corresponding mutant polypeptides unable to bind to GLUT1.

The invention also concerns the use of mutant polypeptides unable to bind to GLUT1 as defined above :

-. as a negative control in the frame of the screening of compounds able to bind specifically to the non mutated corresponding polypeptides, and thus liable to be used in the frame of the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV,

- for the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV.

The invention relates more particularly to the use as defined above, of mutant polypeptides corresponding to the polypeptides defined above, wherein :

- D in position 106 and/or Y in position 114 of the envelope protein of HTLV-1 corresponding to SEQ ID NO : 4,

- D in position 102 and/or Y in position 110 or of HTLV-2 corresponding to SEQ ID NO : 6,

- D in position 106 and/or Y in position 114 or of STLV-1 corresponding to SEQ ID NO : 8,

- D in position 102 and/or Y in position 110 or of STLV-2 corresponding to SEQ ID NO : 10,

- D in position 105 and/or Y in position 113 or of STLV-3 corresponding to SEQ ID NO : 12,

- D in position 18 and/or Y in position 26 of the polypeptides corresponding to SEQ ID NO : 14, 16, 18, 20, 22, and 24,

are substituted by another aminoacid, natural or not, such as mutant polypeptides corresponding to the polypeptides mentioned above wherein said D and/or A residues are substituted by A.

The invention also relates to the use of mutant nucleotide sequences encoding corresponding mutant polypeptides unable to bind to GLUT1 as defined above, for the preparation of transgenic mammal cells expressing said mutant polypeptides, said cells having a negative transdominant effect with regard to PTLV, thus preventing infection and dissemination of this latter in the organism.

The invention also concerns pharmaceutical compositions containing GLUT1 represented by SEQ ID NO : 2, or fragments or sequences derived thereof, said fragments or derived sequences being able to bind to the envelope proteins of the primate T-cell leukemia viruses (PTLV), in association with a pharmaceutically acceptable carrier.

The invention relates more particularly to pharmaceutical compositions containing mutant polypeptides corresponding to the polypeptides defined above, wherein :

- D in position 106 and/or Y in position 114 of the envelope protein of HTLV-1 corresponding to SEQ ID NO : 4,

- D in position 102 and/or Y in position 110 or of HTLV-2 corresponding to SEQ ID NO : 6,

- D in position 105 and/or Y in position 113 or of STLV-3 corresponding to SEQ ID NO : 12,

- D in position 18 and/or Y in position 26, of the polypeptides corresponding to SEQ ID NO : 14, 16, 18, 20, 22, and 24,

are substituted by another aminoacid, natural or not, such as mutant polypeptides corresponding to the polypeptides mentioned above wherein said D and/or A residues are substituted by A,

in association with a pharmaceutically acceptable carrier.

The invention also concerns transgenic mammal cells expressing mutant polypeptides unable to bind to GLUT1 as defined above, said cells having a negative transdominant effect with regard to PTLV, thus preventing infection and dissemination of this latter in the organism.

The invention relates more particularly to pharmaceutical compositions containing transgenic mammal cells as defined above, in association with a pharmaceutically acceptable carrier.

The invention also concerns therapeutic vectors useful for targeting GLUT1 overexpressing cells in pathologies such as defined above, said vectors containing at their surface polypeptide compounds chosen among those defined above, and containing molecules

active against said pathologies, like antitumor molecules, or containing genes in the frame of gene therapy.

The invention relates more particularly to pharmaceutical compositions containing therapeutic vectors as described above, in association with a pharmaceutically acceptable carrier.

The invention also relates to a method for the screening of compounds useful for :

* the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV,

* the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces,

* the *in vitro* detection of GLUT1 on cell surfaces,

said method comprising :

- the contacting of GLUT1 represented by SEQ ID NO : 2, or of fragments or sequences derived thereof, said fragments or derived sequences being able to bind to the envelope proteins of the primate T-cell leukemia viruses (PTLV), or of cells expressing GLUT1, with compounds to be tested,

- the selection of compounds able to bind specifically to GLUT1, or fragments or sequences derived thereof, as for example according to the method mentioned above.

The invention also concerns a method for the *in vitro* diagnosis of cancers, characterized in that it comprises :

- contacting a biological sample (such as biopsies or cells or tissue manifesting or with a suspected aberrant GLUT1 expression profile) from an individual with compounds selected for their ability to bind specifically to GLUT1 as defined above, said compounds being optionally labeled, or susceptible to be recognized by a labeled molecule,

- determining the level of said compounds bound to the cells contained in the biological sample and comparison with the level of binding of said compound to cells contained in the biological sample from an healthy individual.

The invention also relates to a method for the *in vitro* diagnosis of cancers as described above, characterized in that the compounds used are chosen among the compounds defined above selected for their ability to bind specifically to GLUT1.

The invention also concerns a kit for the *in vitro* diagnosis of cancers as described above, comprising compounds selected for their ability to bind specifically to GLUT1 as defined above, said compounds being optionally labeled, and, if necessary reagents for the

detection of the binding of said compounds to GLUT1 initially present on cell surfaces in the biological sample.

The invention is further illustrated with the detailed description hereafter of the determination of GLUT1 as a specific receptor for PTLV RBD.

The human T-cell leukemia virus (HTLV) type 1 and 2 are present in all areas of the world as endemic or sporadic infectious agents [Slattery, 1999]. The etiological role of HTLV-1 in adult T cell leukemia (ATL) and tropical spastic paraparesis/HTLV-associated myelopathy (TSP/HAM) has been well established [Poiesz, 1980; Yoshida, 1982; Gessain, 1985; Osame, 1986]. The apparently restricted tropism of HTLV to T lymphocytes in infected patients[Cavrois, 1996 ; Hanon, 2000] contrasts with the ability of the viral-encoded envelope glycoprotein (Env) to bind to and direct entry into all vertebrate cell types tested in vitro[Sutton, 1996 ; Trejo, 2000; Kim, 2003]. Retroviral infections depend on early interactions between Env and cellular receptors. Identification of cellular receptors and coreceptors for other retroviral envelopes have helped to elucidate certain aspects of retrovirus physiopathology as well as their transmission and spreading within organisms and populations[Berger, 1999; Clapham, 2001; Weiss, 2002]. However, no clear association between HTLV Env and HTLV-associated diseases has been established and the identity of the receptor(s) for HTLV-1 and HTLV-2 Env has remained elusive.

Numerous cell surface components have been shown to play a role in HTLV Env-mediated syncytia formation [Niyogi, 2001; Daenke, 1999; Hildreth, 1997]. Nevertheless, HTLV Env-dependent cell membrane fusion and syncytia formation appear to be distinct from receptor binding per se [Denesvre, 1996; Daenke, 2000; Kim, 2000; Kim, 2003]. The search for HTLV Env receptor has been hindered in part by its ubiquitous presence [Sutton, 1996; Trejo, 2000; Jassal, 2001; Kim, 2003]. Additionally, the induction of rampant syncytium formation in cell culture upon expression of HTLV Env [Hoshino, 1983; Nagy, 1983] has prevented efficient and persistent Env expression. Based on our observation that the HTLV Env amino terminal domain shares striking structural and functional homology with that of murine leukemia viruses (MLV), we defined HTLV Env receptor-binding domain (RBD) and derived HTLV Env-based tools that overcome the problem of syncytia formation [Kim, 2000; Kim, 2003]. We were thus able to follow specific interactions between the Env RBD and a primary HTLV receptor. Using these tools, we have previously shown that the HTLV receptor is expressed on the surface on T lymphocytes, the major HTLV reservoir in vivo, only following T cell receptor activation[Manel, 2003].

Here we describe striking metabolic alterations in cell cultures following expression of HTLV envelopes as well as HTLV receptor binding domains. These alterations are characterized by a defect in the acidification of the cell culture medium associated with a decreased lactate production and a decline in glucose consumption and uptake. These observations as well as the knowledge that Env receptors for the related MLV and most of the gammaretrovirus belong to the family of multiple-membrane spanning transporters[Overbaugh, 2001] prompted us to test ubiquitous lactate and glucose transport-associated molecules as receptors for HTLV Env. We show that the ubiquitous GLUT-1 glucose transporter, present in all vertebrates, is an essential and specific component of the receptor for HTLV. Moreover, interaction of GLUT-1 with the entire HTLV-1 and HTLV-2 envelopes as well as the truncated HTLV-1 and HTLV-2 RBDs alters glucose metabolism.

HTLV envelopes alter lactate metabolism

Cell proliferation in standard culture media is accompanied by acidification of the milieu that translates into a color change from red to yellow tones in the presence of the phenol-red pH indicator. Upon transfection of either highly syncytial HTLV-1 and HTLV-2 envelopes, or a non-syncytial chimeric envelope that harbors the HTLV-1 RBD in a MLV Env backbone (H_{183}FEnv), culture medium did not readily acidify, and harbored red tones for several days post-transfection (fig 1a). Moreover, expression of truncated soluble HTLV RBD proteins fused with either GFP, –HA, or –rFc tags also inhibited medium acidification. In contrast, no envelope construct that lacked HTLV RBD, including different MLV group envelopes, feline, porcine, lentiviral and Jaagsiekte retroviral Envs, as well as VSV-G and Ebola glycoproteins, had this effect. The lack of acidification associated with HTLV-1 or HTLV-2 Env expression was not an indirect consequence of their syncytial activity, since (i) medium acidification was observed in cells expressing a syncytial amphotropic-MLV Env (A-MLV devoid of the R peptide) (fig 1a) and (ii) medium acidification was blocked when HTLV Env was expressed in cells that are resistant to HTLV-Env mediated syncytia formation (NIH3T3 TK$^-$ cells)[Kim, 2003].

Decrease of pH in cell culture is primarily due to extracellular accumulation of lactate [Warburg, 1956]. Lactate is the major byproduct of anaerobic glycolysis *in vitro* and its excretion is mediated by an H+/lactate symporter [Halestrap, 1999]. We monitored lactate content in culture supernatants following transfection of various retroviral envelopes and RBD. Lactate accumulation was consistently 3-fold lower in H_{183}FEnv- and HTLV RBD-transfected cells than in control- or MLV Env-transfected cells (fig 1b). This decrease in

extracellular lactate accumulation after HTLV RBD transfection was DNA dose-dependent. Moreover, we found that the decrease in lactate accumulation following transfection of HTLV RBD was apparent as early as 4 hours after the addition of fresh media (fig 1c).

Receptor binding and lactate metabolism

To examine whether a direct relationship exists between binding of the HTLV envelope receptor and diminished extracellular acidification and lactate accumulation, we attempted to generate HTLV-1 RBD ($H1_{RBD}$) mutants with impaired receptor binding capacities. To this end, mutations resulting in single alanine substitutions were introduced at two different positions in $H1_{RBD}$, D106 and Y114 which are highly conserved among primate T-lymphotropic viruses. Although both D106A and Y114A RBD mutants were expressed and secreted as efficiently as the wild-type $H1_{RBD}$ (fig 2a), they exhibited significantly reduced (D106A) or non detectable (Y114A) binding to the HTLV receptor as detected by FACS analysis (fig 2b). Moreover, perturbations in lactate metabolism correlated with binding to the HTLV receptor: lactate accumulation was not reduced in cells expressing the non-binding Y114A RBD mutant and was minimally reduced in cells harboring the D106 RBD (fig 2c). Similar results were obtained with $H2_{RBD}$ harboring the same allelic mutations. These data favor a direct association between lactate-related metabolic alterations and HTLV Env receptor binding.

Extracellular lactate accumulates in cell cultures following its transport across cellular membranes by the MCT1 monocarboxylate transporter[Garcia, 1994]. Because HTLV and MLV share a common organization of the extracellular envelope [Kim, 2000] and the receptors for MLV Env are multispanning metabolite transporters [Overbaugh, 2001], we assessed whether the HTLV RBD bound to MCT1. Moreover, similar to our previous data concerning expression of the HTLV receptor on T cells [Manel, 2003], expression of MCT1 chaperone CD147 [Kirk, 2000] increases during T cell activation [Kasinrerk, 1992]. However, separate and combined overexpression of MCT1 and CD147 did not result in increased $H1_{RBD}$ binding, arguing against a role for these molecules as receptors for HTLV Env.

HTLV receptor and glucose metabolism

In addition to a decrease in extracellular lactate accumulation, expression of the HTLV RBD also led to decreased intracellular lactate content, indicative of metabolic alterations upstream of lactate transport. In cell cultures, lactate accumulation results from the degradation of glucose during anaerobic glycolysis. Therefore, we assessed whether the

decreased accumulation of lactate observed upon expression of HTLV RBD was linked to glucose metabolism. We measured glucose consumption as normalized to cellular protein content. Glucose consumption of cells expressing an HTLV RBD within the context of the H_{183}FEnv entire envelope or the $H1_{RBD}$ was significantly decreased as compared to control cells (fig 3a) and this defect was detectable as early as 8 hours post transfection. To determine if this decrease in glucose consumption corresponded to a decrease in glucose transport across cellular membrane, we measured 2-deoxyglucose and fructose uptake in control cells and cells expressing HTLV RBD (fig 3b). We observed that expression of either HTLV-1 or HTLV-2 RBD induced an approximatively 4-fold decrease in 2-deoxyglucose uptake, while A-MLV RBD had only a minor effect. Inhibitors of glucose uptake, cytochalasin B and phloterin, also inhibited glucose uptake. Theses results were also true for 3-O-methylglucose transport. Fructose uptake in the same cells was not altered by the presence of HTLV-1 nor HTLV-2 RBD however A-MLV RBD induced a slight decreased. We next evaluated the effect of glucose deprivation on the availability of the HTLV receptor in both adherent human 293T cells and suspension Jurkat T cells. After overnight culture of cells in the absence of glucose, binding of $H1_{RBD}$ was consistently increased by 2-fold in both cell types (fig 3c). This effect of glucose deprivation was specific to HTLV as amphotropic MLV RBD (A_{RBD}) binding was only marginally affected (fig 3c). This phenomenon is reminiscent of a general metabolite transport feedback loop, whereby transporter availability at the cell surface increases upon substrate starvation [Martineau, 1972].

HTLV envelopes bind glucose transporter-1

A simple model whereby the HTLV envelope inhibits glucose consumption via direct binding to a glucose transporter can explain the metabolic effects described above. Upon evaluation of the different glucose transporter candidates, GLUT-1 appears to be the only one encompassing all the known properties of the HTLV receptor. Indeed, GLUT-1 expression is increased upon glucose deprivation and is transports glucose in all vertebrate cells [Mueckler, 1985], while fructose is transported by GLUT-5. Furthermore, GLUT-1 is not expressed on resting primary T cells and its expression is induced upon T cell activation [Rathmell, 2000; Chakrabarti, 1994] with kinetics that are strikingly similar to what we have reported for the HTLV receptor [Manel, 2003]. Since human but not murine erythrocytes have been described to be the cells exhibiting the highest concentration of GLUT-1 [Mueckler, 1994], we evaluated HTLV receptor availability on freshly isolated red blood cells. Binding of $H1_{RBD}$ on human erythrocytes was strikingly efficient, reaching levels higher than those observed on

any other tested cell type, whereas A_{RBD} binding to erythrocytes was minimal (fig 4a). On murine erythrocytes however, no significant $H1_{RBD}$ binding could be detected, despite a similar A_{RBD} binding on murine and human erythrocytes. Furthermore, primary human hepatocytes do not express GLUT-1. Accordingly, we were unable to detecte $H1_{RBD}$ binding to human primary hepatocytes, while A_{RBD} binding could be readily detected.

In order to directly test the ability of HTLV envelopes to bind GLUT-1, we derived a tagged GLUT-1 expression vector and overexpressed this protein in HeLa cells. Both $H1_{RBD}$ and $H2_{RBD}$ binding was dramatically increased upon GLUT-1 overexpression (fig 4b). This interaction was specific as the HTLV-2 binding-defective mutant, D102A, as well as its HTLV-1 counterpart, D106A, did not bind GLUT-1 (fig 4b). Furthermore, $H1_{RBD}$ and $H2_{RBD}$ binding remained at background levels upon overexpression of the amphotropic MLV envelope receptor, the inorganic phosphate transporter PiT2 [Miller, 1994]. Conversely, binding of A_{RBD} was not increased after GLUT-1 overexpression but as expected, this interaction was increased upon transfection of PiT2 (fig 4b). GLUT-3 is the closest isoform to GLUT-1, and transports glucose with kinetics similar to that of GLUT-1. Thus, we derived a tagged GLUT-3 expression vector. Albeit similar overexpression levels of GLUT-1 and GLUT-3 in 293T cells, GLUT-3 did not induce any increase in $H1_{RBD}$ binding (fig 4c), suggesting that increase $H1_{RBD}$ binding in cells overexpressing GLUT-1 is not an indirect consequence of increased glucose uptake. To determine if GLUT-1 transfected cells were directly responsible for the observed increased in $H1_{RBD}$ binding, we derived fluorescent tagged GLUT-1 and GLUT-3 to uniquevocally identity GLUT-overexpressing cells in the course of our FACS analysis. In this context, only cells overexpressing GLUT-1-DsRed2 displayed an significant increase in $H1_{RBD}$ binding, while overexpressing GLUT-3-DsRed2 had no effect on $H1_{RBD}$ binding (fig4d). Consequently, we tested if HTLV glycoproteins directly interacts with GLUT-1 proteins. To this end, we evaluated the ability of $H1_{RBD}$ to immunoprecipitate GLUT-1. As shown on fig 4e, GLUT-1 could be readily detected upon immunoprecipitation with anti-rabbit-Fc-beads when it was co-expressed with $H1_{RBD}$, but could not be detected when expressed alone or with the $H1_{RBD}$ Y114A mutant. Moreover, a GFP-tagged HTLV-2 RBD colocalized with GLUT-1 but not with PiT2 as assessed by fluorescence microscopy. Therefore, the GLUT-1 glucose transporter is an essential component of the HTLV envelope receptor.

Interaction of GLUT-1 with its ligand cytochalasin B inhibits glucose transport [Kasahara, 1977]. Since we showed that binding of HTLV envelopes to GLUT-1 inhibits glucose consumption and uptake, we tested whether cytochalasin B would abrogate HTLV

RBD binding. Indeed, cytochalasin B treatment of Jurkat T cells dramatically inhibited binding of $H1_{RBD}$, whereas binding of A_{RBD} was not affected (fig 5a). Thus, GLUT-1 directed glucose transport as well as binding of HTLV envelopes to GLUT-1 are similarly inhibited by the cytochalasin B ligand. Altogether, these data demonstrate that GLUT-1 is a receptor for HTLV envelopes.

Viral receptor permits entry and thus infection. No cellular system currently exists that lacks GLUT-1 expression. Thus, we developed a system in which HTLV infection is specifically inhibited at the level of envelope-receptor interaction. In this system, over-expression of HTLV-2 RBD interferes with infecting incoming HTLV particles and specifically decreases HTLV titers by at least 2 logs, while no effect is detected on control A-MLV titers. To determine if GLUT-1 is an entry receptor for HTLV, we overexpressed GLUT-1, GLUT-3 or Pit2 in addition to the interfering $H2_{RBD}$. While Pit2 and GLUT-3 had no effect on HTLV titers, GLUT-1 completely alleviated the interference to infection induced by $H2_{RBD}$ (fig 5b). Interestingly, both GLUT-1 and GLUT-3, but not Pit2, alleviated the alteration of glucose metabolism induced by the HTLV RBD. Thus, GLUT-1 is an entry receptor for HTLV.

Discussion

Here we show that HTLV-1 and -2 envelopes interact with GLUT-1 through their receptor binding domains. This interaction strongly inhibits glucose consumption and glucose uptake, leading to decreased lactate production and a block in extracellular milieu acidification. Mutations that specifically altered receptor binding of both HTLV-1 and 2 envelopes released the block in glucose consumption, indicative of a direct correlation between receptor binding determinants in the HTLV envelopes and glucose transport. Glucose starvation was rapidly followed by increased binding of HTLV envelopes, highlighting a nutrient-sensing negative feedback loop between glucose availability and cell surface HTLV receptor expression. Further evidence converged to identify GLUT-1 as the receptor, including increased binding of HTLV RBD upon overexpression of GLUT-1 but not GLUT-3, immunoprecipitation of GLUT-1 by $H1_{RBD}$ but not the receptor-binding mutant $H1_{RBD}$ Y114A, uppermost binding of HTLV RBD on human erythrocytes, where GLUT-1 is the major glucose transporter isoform, and no binding of HTLV RBD on human primary hepatocytes and murine erythrocytes, where GLUT-1 is minimally expressed. Finally, GLUT-1 could specifically alleviate interference to infection induced by HTLV RBD. GLUT-1 fits all other known properties of the HTLV receptor. Indeed, as previously demonstrated for the

HTLV receptor [Manel, 2003], GLUT-1, but not the GLUT 2-4 isoforms, is not expressed on resting T lymphocytes [Chakrabarti, 1994; Korgun, 2002] and is induced upon immunological [Frauwirth, 2002; Yu, 2003] or pharmacological [Chakrabarti, 1994] activation. Moreover, GLUT-1 orthologues are highly conserved among vertebrates, but are highly divergent between vertebrates and insects [Escher, 1999].

GLUT-1 is thus a new member of the multimembrane spanning metabolite transporters that serve as receptors for retroviral envelopes. Interestingly, until now, all envelopes that recognize these receptors have been encoded by retroviruses that have a so-called simple genetic organization, such as MLV, feline leukemia viruses, porcine endogenous retrovirus and the gibbon ape leukemia virus [Overbaugh, 2001], whereas HTLV belongs to the so-called complex retroviruses which code for several additional regulatory proteins. However, we have shown that in contrast to the wide phylogenetic divergence of their genomic RNA, the envelopes of HTLV and MLV share a similar modular organization with some highly conserved amino acid motifs in their respective receptor binding domains[Kim, 2000].

Cell-to-cell contact appears to be required for HTLV transmission, and the cytoskeleton appears to play a major role in this process [Igakura, 2003]. Indeed, we observed that the HTLV receptor, despite pancellular expression, is specifically concentrated to mobile membrane regions and cell-to-cell contact areas. It should therefore be expected that the HTLV envelope receptor is associated to the cytoskeleton. Importantly, a cytoplasmic-binding partner of GLUT-1, GLUT1CBP, which encodes a PDZ domain, has been reported to link GLUT-1 to the cytoskeleton [Bunn, 1999]. It will therefore be interesting to evaluate the respective roles of the HTLV envelope, its cytoskeleton-associated cellular partners, such as GLUT-1, GLUT1CBP and their immediate interacting cell components.

Because expression of the HTLV receptor is induced upon glucose starvation, transmission of HTLV may be more efficient in cells that are locally starved for glucose, such as lymphocytes in lymph nodes [Yu, 2003]. Furthermore, the ability of circulating erythrocytes to dock HTLV, as shown here, might provide a means to distribute HTLV to such tissues.

The identification of GLUT-1 as a receptor for HTLV envelopes provides additional clues as to the ubiquitous in vitro expression of the receptor on cell lines and the paradoxical restriction of HTLV tropism to T lymphocytes in vivo. Rapid and dramatic metabolic alterations associated with the blockade of glucose consumption are likely to take place upon expression of the HTLV envelope in vivo, early after infection. Therefore, we propose that in vivo, HTLV infection initially spreads with a large tropism, however early after infection the

vast majority of cells that are highly dependent on GLUT-1 activity are rapidly eliminated. In contrast, resting T lymphocytes that have an extremely low metabolic rate and as such are much less dependent on glucose uptake, can tolerate this effect and are therefore maintained in vivo. Furthermore, local imbalances in the access to glucose following HTLV infection may lead to specific physiological alterations [Akaoka, 2001]. In this regard, it will be of interest to study the potential relationship between HTLV-associated neuropathologies and the specific dependence of neurons on GLUT-1 mediated glucose consumption [Siegel, 1998].

Methods.

Cell culture. 293T human embryonic kidney and HeLa cervical carcinoma cells were grown in Dulbecco's modified Eagle medium (DMEM) with high glucose (4.5 g/l) and Jurkat T-cells were grown in RPMI supplemented with 10% fetal bovine serum (FBS) at 37°C in a 5% CO2-95% air atmosphere. For glucose starvation experiments, cells were grown in either glucose-free DMEM (Life Technologies) or glucose-free RPMI - (Dutscher) with 10% dialyzed FBS (Life Technologies) and glucose (1g/l) was supplemented when indicated.

Expression vectors. Full length envelope expression vectors for HTLV-1 (pCEL/2[Denesvre, 1995]) and Friend ecotropic MLV (pCEL/F [Denesvre, 1995]), have been previously described. For the HTLV-2 envelope, a fragment from pHTE2 [Rosenberg, 1998] encompassing the *tax*, *rex* and *env* genes and the 3' LTR was inserted in the pCSI [Battini, 1999] vector (pCSIX.H2). Full length envelope expression vectors for amphotropic MLV (pCSI.A), or devoid of its R peptide (pCSI.AΔR), and H_{183}FEnv that contains the N-terminal 183 amino acids of the HTLV-1 receptor-binding domain in the F-MLV envelope background, as well as truncated envelope expression vectors, derived from pCSI and encoding either of the first 215 residues of HTLV-1 SU ($H1_{RBD}$), the first 178 residues of HTLV2-SU ($H2_{RBD}$) or the first 397 residues of the amphotropic murine leukemia virus (MLV) SU (A_{RBD}), fused to a C-terminal rabbit IgG Fc tag (rFc) or to EGFP ($H2_{RBD}$-GFP). All point mutations introduced in HTLV-1 and -2 RBD constructs were generated using the quickchange site-directed mutagenesis method and mutations were verified by sequencing. Human *Glut-1* and *Glut*-3 cDNA were amplified by PCR from the pLib HeLa cDNA library (Clontech), and inserted into pCHIX, a modified version of the pCSI vector that contains a cassette comprising a factor Xa cleavage site, two copies of the hemagglutinin (HA) tag, and a histidine tag. The resulting construct (pCHIX.hGLUT1) encodes a GLUT-1 protein with a HA-His tag at the C-terminal end. GLUT-1 and GLUT-3 were also inserted in a modified

pCSI vector containing a DsRed2 C-terminal tag. Similarly, human CD147 was amplified from 293T total RNA by RT-PCR and inserted into the pCHIX backbone in frame with the HA-His tag (pCHIX.hCD147).

Envelope expression and metabolic measurements. 293T cells were transfected with the various envelope expression vectors using a modified version of the calcium phosphate method. After an overnight transfection, cells were washed in phosphate-buffered saline (PBS) and fresh medium was added. Media were harvested at the indicated time points, filtered through a 0.45-µm pore-size filter, and lactate and glucose were measured with enzymatic diagnostic kits (Sigma). Values were normalized to cellular protein content using the Bradford assay (Sigma) after solubilization of cells in lysis buffer (50 mM Tris-HCl pH 8.0, 150 mM NaCl, 0.1% sodium dodecyl sulfate, 1.0% Nonidet P-40, 0.5% deoxycholate) and clarification by centrifugation.

Assay of hexose uptake. 2-deoxy-D[1-^{3}H]glucose, D[U-^{14}C]fructose and 3-O-[^{14}C]methyl-D-glucose were obtained from Amersham. Hexose uptake assay were adapted from Harrison et al(REF HARRISON 1991). After transfection, approximatively 250,000 were seeded/well in 24-well plates. The next day, cells were washed two times in PBS, incubated in serum-free DMEM, washed one time in serum-free glucose-free DMEM, and incubated for 20' in 500 µl serum-free glucose-free DMEM modulo inhibitors (20 µM cytochalasin B, 300 µM phloretin; SIGMA). Uptake was initiated by adding labeled hexoses to a final concentration of 0,1 mM (2 µCi/ml for 2-2-deoxy-D[1-^{3}H]glucose and 0,2 µCi/ml for D[U-^{14}C]fructose and 3-O-[^{14}C]methyl-D-glucose) and cells were incubated for 5' additional minutes. Cells were then resuspended in 500 µl cold serum-free glucose-free DMEM, wash one time in serum-free glucose-free DMEM, and solubilized in 400 µl of 0,1% SDS. 3 µl was used for Bradford normalization, while the rest was used for detection of either ^{3}H or ^{14}C by liquid scintillation in a Beckman counter.

Western blots. Culture media (10 µl) from 293T cells expressing wild type or mutant HTLV-1 RBDs, and/or GLUT-1or GLUT-3 expression vecotor. were subjected to electrophoresis on SDS–15% acrylamide gels, transferred onto nitrocellulose (Protran; Schleicher & Schuell), blocked in PBS containing 5% powdered milk and 0.5% Tween 20, probed with either a 1:5000 dilution of horseradish peroxidase-conjugated anti-rabbit immunoglobulin or 1:2000 dilution of anti-HA 12CA5 (Roche) monoclonal antibody followed by a 1:5000 dilution of horseradish peroxidase-conjugated anti-mouse immunoglobulin, and visualized using an enhanced chemiluminescence kit (Amersham).

Binding assays. Binding assays were carried out as previously described [Manel, 2003]. Briefly, 5 x 10^5 cells (293T, HeLa, Jurkat or freshly isolated human erythrocytes) were incubated with 500 µl of $H1_{RBD}$, $H2_{RBD}$ or A_{RBD} supernatants for 30 min at 37°C, washed with PBA (1% BSA, 0.1% sodium azide in PBS), and incubated with a sheep anti-rabbit IgG antibody conjugated to fluorescein isothiocyanate (Sigma). When indicated, cytochalasin B (20 µM; Sigma) was added to cells for 1 hour prior to binding analyses. Binding was analyzed on a FACSCalibur (Becton Dickinson) and data analysis was performed using CellQuest (Becton Dickinson) and WinMDI (Scripps) softwares.

Infections. 293T cells were transfected in 6-wells plate, and one day after transfection, medium was replaced by high glucose DMEM supplemented with fructose (5 g/l) and non-essential amino acids. The next day, infection was initiated by adding supernatants containing MLV particles pseuodtyped with either HTLV-2 or A-MLV envelopes. The following day, fresh medim was added, and 24 hours later cells were fixed and stained for alkaline phosphatase activity and dark focus of infection were counted. Viral particles were obtained by transfecting 293T cells with pLAPSN, pGagPoule and either pCSIX.H2 or pCSI.A, and harvesting the 0.45µm-filtered supernatants 24 hours latter.

FIGURE LEGENDS

Figure 1 Expression of the HTLV receptor-binding domain alters cellular metabolism. **a**, Medium acidification and syncytia formation in 293T cells one day post-transfection with control DNA or Env expression vectors, including syncytial wild-type HTLV-1 Env and HTLV-2 Env, a non-syncytial chimeric H_{183}FEnv, and syncytial A-MLV ΔR Env. **b**, Extracellular lactate and glucose in the culture medium of 293T cells were measured two days following transfection with an irrelevant DNA (control), F-MLV Env, H_{183}FEnv, HTLV-1 RBD ($H1_{RBD}$) or amphotropic MLV RBD (A_{RBD}) expression vectors. Lactate and glucose concentrations were normalized to cellular protein content. **c**, 2-deoxyglucose and fructose uptake following transfection of 293T with an irrelevant DNA (control), $H1_{RBD}$, $H2_{RBD}$ or A_{RBD} expression vectors. Control cells were also incubated with glucose transporter inhibitors cytochalasin and phloretin. Data are the means of triplicate measures and are representative of two to three independent experiments. **d**, Expression of the HTLV and amphotropic-MLV receptors on 293T (1) and Jurkat T (2) cells cultured overnight in the presence or absence of glucose was monitored by binding of $H1_{RBD}$ and A_{RBD}, respectively.

Figure 2 HTLV recepetor properties correlates with GLUT1 properties. **a,** Expression of the HTLV and amphotropic-MLV receptors at the surface of human and murine erythrocytes, as well as human primary hepatocytes. **b,** $H1_{RBD}$ and A_{RBD} binding to Jurkat cells in the absence or presence of the Glut-1 inhibitor cytochalasin B.

Figure 3 HTLV receptor-binding correlates with altered lactate metabolism. **a,** Expression of $H1_{RBD}$ and the derived mutants D106A and Y114A was monitored by Western blot analysis of the supernatants of 293T cells following transfection with the various expression plasmids. **b,** Binding of $H1_{RBD}$ and the D106A and Y114A mutants to the HTLV receptor on HeLa cells. **c,** Extracellular lactate in the medium of 293T cells one day post transfection with an irrelevant DNA (control), $H1_{RBD}$ or the $H1_{RBD}$ D106A and Y114A mutants. Data are representative of three independent experiments.

Figure 4 GLUT-1 is a receptor for HTLV envelopes. **a,** Binding of $H1_{RBD}$, $H2_{RBD}$, $H2_{RBD}$ D102A mutant, and A_{RBD} to control 293T cells or 293T cells overexpressing either GLUT-1 or PiT2. **b,** Binding of $H2_{RBD}$-EGFP to cells overexpressing GLUT-1-HA or GLUT-3-HA, and corresponding immuoblots using an anti-HA antibody. **c,** Immunprecipitation of GLUT-1-HA from 293T cells transfected with either an irrelevant construct, GLUT-1 alone, H1RBD alone, H1RBD Y114A alone, GLUT-1 with $H1_{RBD}$ or GLUT-1 with $H1_{RBD}$ Y114A expression vectors. Immunoprecipitation was performed using anti-rabbit-Fc beads and probed with an anti-HA antibody. Total cell extracts were blotted using an anti-rabbit Fc or an anti-HA antibody.

Figure 5 GLUT-1 is an entry receptor for HTLV. Infections titer of MLV particles pseudotypes with HTLV-2 or A-MLV envelopes on 293T cells following transfection of an irrelevant or interfering $H2_{RBD}$ expression vectors alone or in addition to GLUT-1, GLUT-3 or Pit2 expression vectors.

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CLAIMS

1. Use of the ubiquitous vertebrate glucose transporter GLUT1 represented by SEQ ID NO : 2, or of fragments or sequences derived thereof, said fragments or derived sequences being able to bind to the envelope proteins of the primate T-cell leukemia viruses (PTLV), or of cells expressing GLUT1, for:

- the screening of compounds useful for :

  * the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV,

  * the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces,

  * the *in vitro* detection of GLUT1 on cell surfaces,

  said compounds being selected for their ability to bind specifically to said GLUT1,

- the detection, concentration, and/or purification of PTLV or variants thereof, or of PTLV envelope proteins, or fragments thereof,

- the preparation of drugs for the prevention or the treatment of pathologies either linked to an infection of an individual or an animal with a PTLV, such as HTLV-1, HTLV-2, STLV-1, STLV-2, STLV-3, or their variants, or linked to the presence of PTLV SU-related sequences in such individuals or animals,

- the *in vitro* diagnosis of cancers, when used as a tumor marker.

2. Use according to claim 1, of fragments of GLUT1 chosen among the followings :

- SEQ ID NO : 25 : NAPQKVIEEFY
- SEQ ID NO : 26 : NQTWVHRYGESILPTTLTTLWS
- SEQ ID NO : 27 : KSFEMLILGR
- SEQ ID NO : 28 : DSIMGNKDL
- SEQ ID NO : 29 : YSTSIFEKAGVQQP
- SEQ ID NO : 30 : EQLPWMSYLS
- SEQ ID NO : 31 : QYVEQLC

3. Use of compounds selected for their ability to bind specifically to GLUT1 as defined in claim 1, for the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV, such as pathologies corresponding to adult T cell leukemia (ATL), HTLV-I-associated myelopathy/tropical spastic paraparesis

(HAM/TSP), as well as other HTLV-associated syndromes such as large granular lymphocyte (LGL) leukaemia, uveitis, infective dermatitis, arthropathies, cutaneous T cell lymphoma (mycosis fungoides), polymyositis.

4. Use of compounds according to claim 3, chosen among androgenic steroids, cytochalasin B, forskolin, dipyridamole, isobutylmethylxanthine, ethanol, genistein, cadmium, barbiturate, dehydroascorbic acid, tricyclic antidepressants, oestradiol, anti-oestrogens, faslodex (ICI 182780), tamoxifen, gamma agonists of peroxisome proliferator-activated receptors (PPAR) such as thiazolidinedione, troglitazone, pioglitazone, ro siglitazone.

5. Use of compounds selected for their ability to bind specifically to GLUT1 in the conditions defined in claim 1, for the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces, such as :

- cancers, such as squamous cell carcinoma, hypopharyngeal carcinoma, breast cancer, cervical carinoma, ovarian carcinoma, pancreatic cancer, insulinoma,
- inflammatory conditions,
- immune or auto-immune diseases, such as autoimmune myocarditis, or in the frame of CD28 T-cell activation, or in the frame of immunomodulation,
- disorders of the central nervous system, such as facilitated glucose transporter protein type 1 (GLUT1) deficiency syndrome.

6. Use according to claim 5, of compounds chosen among the followings :

- polypeptides compounds corresponding to the envelope proteins of PTLV, or fragments or sequences derived thereof, said fragments or derived sequences being able to bind to GLUT1;
- glucose or derivatives such as galactose, 2-fluorodeoxyglucose, 2-deoxyglucose, 3-O-methylglucose
- androgenic steroids, cytochalasin B, forskolin, dipyridamole, isobutylmethylxanthine, ethanol, genistein, cadmium, barbiturate, dehydroascorbic acid, tricyclic antidepressants, oestradiol, anti-oestrogens, faslodex (ICI 182780), tamoxifen, gamma agonists of peroxisome proliferator-activated receptors (PPAR) such as thiazolidinedione, troglitazone, pioglitazone, ro siglitazone.

7. Use according to claim 5 or 6, of polypeptides compounds chosen among the followings :

- the envelope protein of HTLV-1 corresponding to SEQ ID NO : 4, or of HTLV-2 corresponding to SEQ ID NO : 6, or of STLV-1 corresponding to SEQ ID NO : 8, or of STLV-2 corresponding to SEQ ID NO : 10, or of STLV-3 corresponding to SEQ ID NO : 12,

- fragments of the envelope proteins of PTLV, said fragments corresponding to polypeptides delimited in their N-terminal extremity by the amino acid located in position 1 to 90, or in position 75 to 90, and in their C-terminal extremity by the amino acid located in position 135 to 245, or in position 135 to 150, of said envelope proteins of PTLV, such as SEQ ID NO : 4, 6, 8, 10, 12,

- fragments of the envelope proteins of PTLV, said fragments corresponding to the following polypeptides :

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 83 to 89, and in its C-terminal extremity by the amino acid located in position 139 to 145, of the envelope protein of the strain MT-2 of HTLV-1 corresponding to SEQ ID NO : 4,

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 79 to 85, and in its C-terminal extremity by the amino acid located in position 135 to 141, of the envelope protein of the strain NRA of HTLV-2 corresponding to SEQ ID NO : 6,

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 83 to 89, and in its C-terminal extremity by the amino acid located in position 139 to 145, of the envelope protein of STLV-1 corresponding to SEQ ID NO : 8,

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 79 to 85, and in its C-terminal extremity by the amino acid located in position 135 to 141, of the envelope protein of STLV-2 corresponding to SEQ ID NO : 10,

* the polypeptide delimited in its N-terminal extremity by the amino acid located in position 82 to 88, and in its C-terminal extremity by the amino acid located in position 138 to 144, of the envelope protein of STLV-3 corresponding to SEQ ID NO : 12,

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 14,

I K K P N P N G G G Y Y L A S Y S D
P C S L K C P Y L G C Q S W T C P Y
T G A V S S P Y W K F Q Q D V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 16,

V K K P N R N G G G Y Y L A S Y S D
P C S L K C P Y L G C Q S W T C P Y
T G A V S S P Y W K F Q Q D V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 18,

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T G A V S S P Y W K F Q Q D V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 20,

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P C S L K C P Y L G C Q S W T C P Y
T G P V S S P Y W K F Q Q D V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-1, said polypeptide having the following sequence SEQ ID NO : 22,

I K K P N R N G G G Y H S A S Y S D P
C S L K C P Y L G C Q S W T C P Y A G
A V S S P Y W K F Q Q D V N F T Q E V

* the polypeptide corresponding to the envelope protein of a variant of HTLV-2, said polypeptide having the following sequence SEQ ID NO : 24,

I R K P N R Q G L G Y Y S P S Y N D
P C S L Q C P Y L G S Q S W T C P Y
T A P V S T P S W N F H S D V

8. Use of compounds selected for their ability to bind specifically to GLUT1 in the conditions defined in claim 1, for the *in vitro* detection of GLUT1 on cell surfaces in the frame of processes for the *in vitro* diagnosis of cancers, said processes comprising the following steps :

- contacting a biological sample from an individual with a compound as defined above, said compound being optionally labeled, or susceptible to be recognized by a labeled molecule,

- determining the level of said compound bound to the cells contained in the biological sample and comparison with the level of binding of said compound to cells contained in the biological sample from an healthy individual.

9. Use according to claim 8, characterized in that the compounds used are chosen among those defined in claims 4, 6, and 7.

10. Use according to claim 5, of polypeptide compounds chosen among those defined in claims 6 and 7, or of nucleotide sequences encoding said polypeptides, for the preparation of vectors containing at their surface said polypeptides, said vectors being useful for targeting GLUT1 overexpressing cells in pathologies such as defined in claim 5, and more particularly tumor cells, or cells involved in the inflammatory mechanism, or activated cells of the immune system, or cells of the central nervous system, said vectors containing molecules active against said pathologies, like antitumor molecules, or containing genes in the frame of gene therapy.

11. Use of nucleotide sequences encoding polypeptides compounds selected for their ability to bind specifically to GLUT1 in the conditions defined in claim 1, such as nucleotide sequences encoding the polypeptides defined in claim 7, or fragments thereof, for the preparation, by substitution of one or several nucleotides of said nucleotide sequences, of mutant nucleotide sequences encoding corresponding mutant polypeptides unable to bind to GLUT1.

12. Use of mutant polypeptides unable to bind to GLUT1 as defined in claim 11 :

- as a negative control in the frame of the screening of compounds able to bind specifically to the non mutated corresponding polypeptides, and thus liable to be used in the frame of the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV,
- for the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV.

13. Use according to claim 12, of mutant polypeptides corresponding to the polypeptides defined in claim 7, wherein :

- D in position 106 and/or Y in position 114 of the envelope protein of HTLV-1 corresponding to SEQ ID NO : 4,
- D in position 102 and/or Y in position 110 or of HTLV-2 corresponding to SEQ ID NO : 6,

- D in position 105 and/or Y in position 113 or of STLV-3 corresponding to SEQ ID NO : 12,

- D in position 18 and/or Y in position 26 of the polypeptides corresponding to SEQ ID NO : 14, 16, 18, 20, 22, and 24,

are substituted by another aminoacid, natural or not, such as mutant polypeptides corresponding to the polypeptides mentioned above wherein said D and/or A residues are substituted by A.

14. Use of mutant nucleotide sequences encoding corresponding mutant polypeptides unable to bind to GLUT1 as defined in claims 11 to 13, for the preparation of transgenic mammal cells expressing said mutant polypeptides, said cells having a negative transdominant effect with regard to PTLV, thus preventing infection and dissemination of this latter in the organism.

15. Pharmaceutical compositions containing GLUT1 represented by SEQ ID NO : 2, or fragments or sequences derived thereof, said fragments or derived sequences being able to bind to the envelope proteins of the primate T-cell leukemia viruses (PTLV), in association with a pharmaceutically acceptable carrier.

16. Pharmaceutical compositions containing mutant polypeptides corresponding to the polypeptides defined in claim 7, wherein :

- D in position 106 and/or Y in position 114 of the envelope protein of HTLV-1 corresponding to SEQ ID NO : 4,

- D in position 102 and/or Y in position 110 or of HTLV-2 corresponding to SEQ ID NO : 6,

- D in position 105 and/or Y in position 113 or of STLV-3 corresponding to SEQ ID NO : 12,

- D in position 18 and/or Y in position 26 the polypeptides corresponding to SEQ ID NO : 14, 16, 18, 20, 22, and 24,

are substituted by another aminoacid, natural or not, such as mutant polypeptides corresponding to the polypeptides mentioned above wherein said D and/or A residues are substituted by A,

in association with a pharmaceutically acceptable carrier.

17. Transgenic mammal cells expressing mutant polypeptides unable to bind to GLUT1 as defined in claims 11 to 13, said cells having a negative transdominant effect with regard to PTLV, thus preventing infection and dissemination of this latter in the organism.

18. Pharmaceutical compositions containing transgenic mammal cells according to claim 17, in association with a pharmaceutically acceptable carrier.

19. Therapeutic vectors useful for targeting GLUT1 overexpressing cells in pathologies such as defined in claim 5, said vectors containing at their surface polypeptide compounds chosen among those defined in claims 6 and 7, and containing molecules active against said pathologies, like antitumor molecules, or containing genes in the frame of gene therapy.

20. Pharmaceutical compositions containing therapeutic vectors according to claim 19, in association with a pharmaceutically acceptable carrier.

21. Method for the screening of compounds useful for :

* the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV,

* the preparation of drugs for the prevention or the treatment of pathologies linked to an overexpression of GLUT1 on cell surfaces,

* the *in vitro* detection of GLUT1 on cell surfaces,

said method comprising :

- the contacting of GLUT1 represented by SEQ ID NO : 2, or of fragments or sequences derived thereof, said fragments or derived sequences being able to bind to the envelope proteins of the primate T-cell leukemia viruses (PTLV), or of cells expressing GLUT1, with compounds to be tested,

- the selection of compounds able to bind specifically to GLUT1, or fragments or sequences derived thereof.

22. Method for the *in vitro* diagnosis of cancers, characterized in that it comprises :

- contacting a biological sample from an individual with compounds selected for their ability to bind specifically to GLUT1 in the conditions defined in claim 1, said compounds being optionally labeled, or susceptible to be recognized by a labeled molecule,

- determining the level of said compounds bound to the cells contained in the biological sample and comparison with the level of binding of said compound to cells contained in the biological sample from an healthy individual.

23. Method for the *in vitro* diagnosis of cancers according to claim 22, characterized in that the compounds used are chosen among those defined in claims 4, 6, and 7.

24. Kit for the *in vitro* diagnosis of cancers according to the method of claim 22 or 23, comprising compounds selected for their ability to bind specifically to GLUT1 in the conditions defined in claim 1, said compounds being optionally labeled, such as compounds defined in claims 4, 6, and 7, and, if necessary reagents for the detection of the binding of said compounds to GLUT1 initially present on cell surfaces in the biological sample.

ABSTRACT

GLUT-1 AS A RECEPTOR FOR HTLV ENVELOPES AND ITS USES

The invention relates to the use of the ubiquitous vertebrate glucose transporter GLUT1, or of fragments or sequences derived thereof, for the *in vitro* diagnosis of cancers, when used as a tumor marker, or for the screening of compounds useful for the preparation of drugs for the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV, or pathologies linked to an overexpression of GLUT1 on cell surfaces, or the *in vitro* detection of GLUT1 on cell surfaces. The invention also relates to pharmaceutical compositions containing GLUT1, or fragments or sequences derived thereof, and to their uses such as in the frame of the prevention or the treatment of pathologies linked to an infection of an individual with a PTLV.

(no drawing)

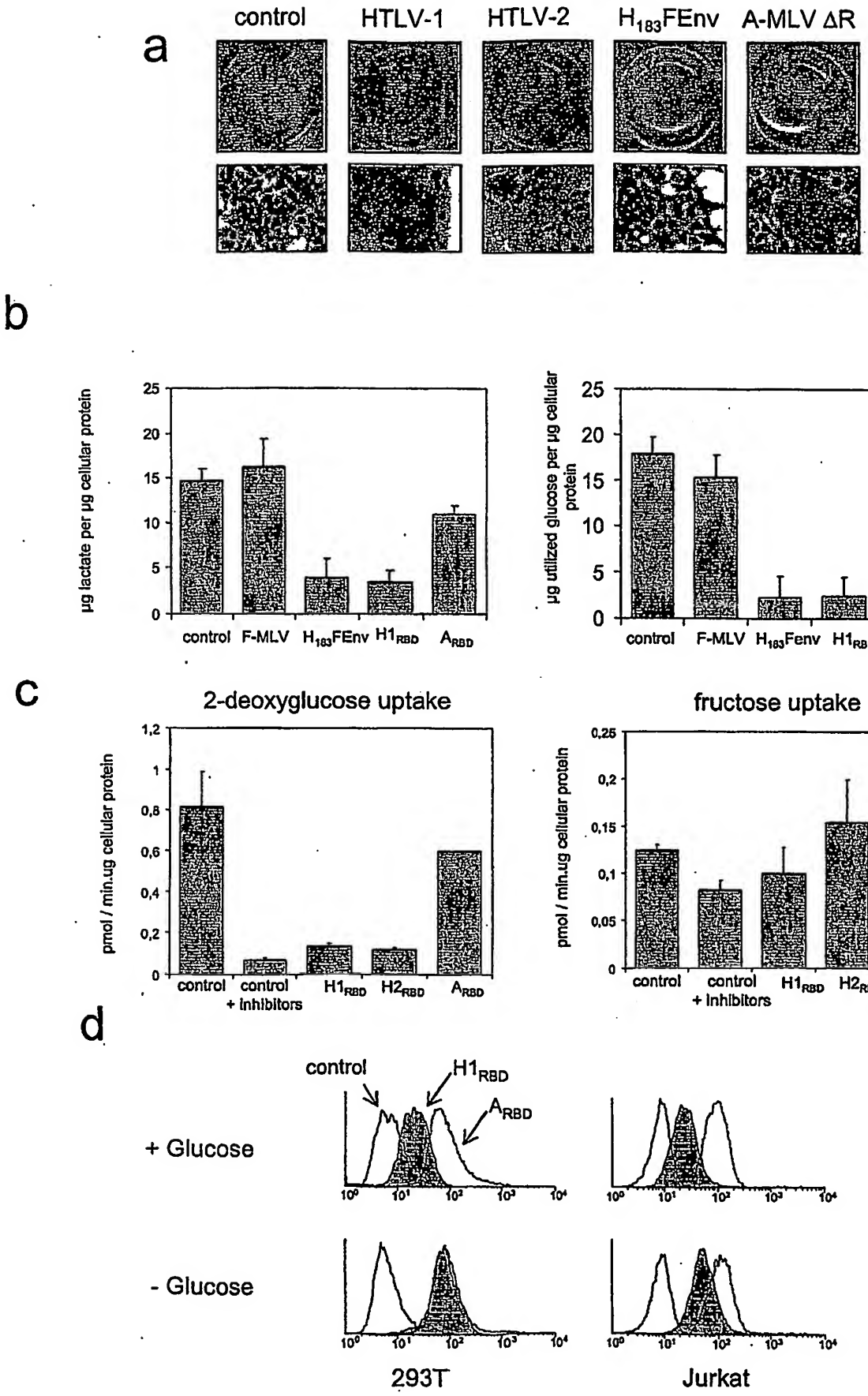
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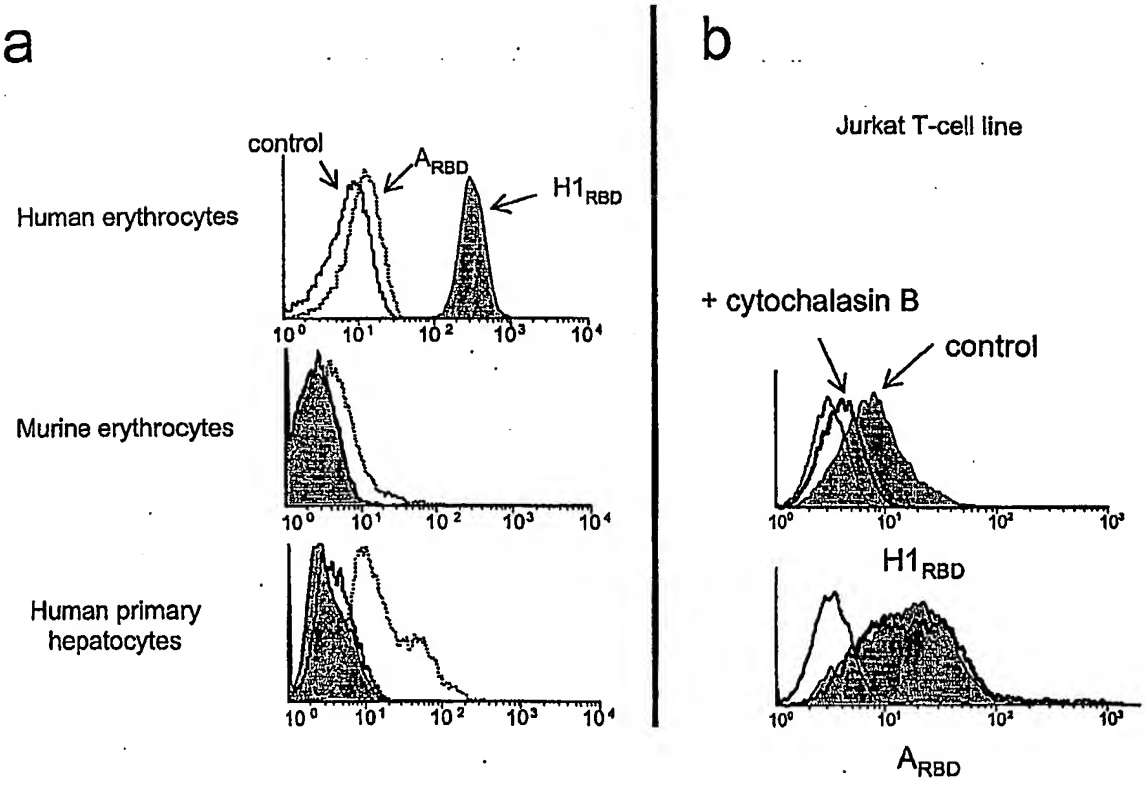
Figure 1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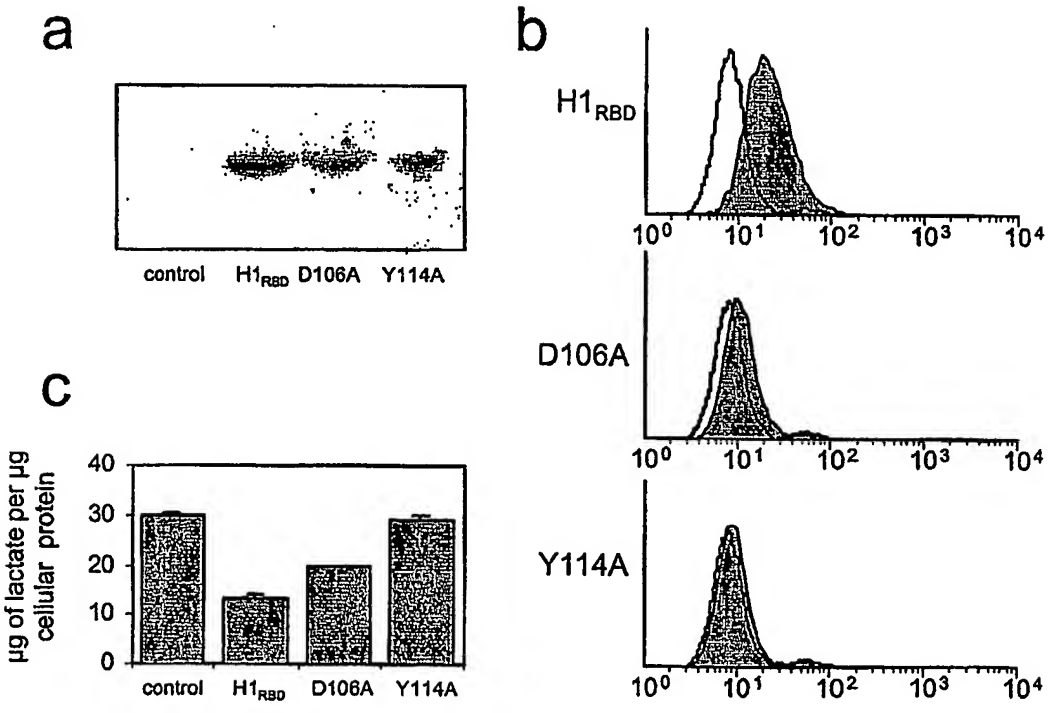
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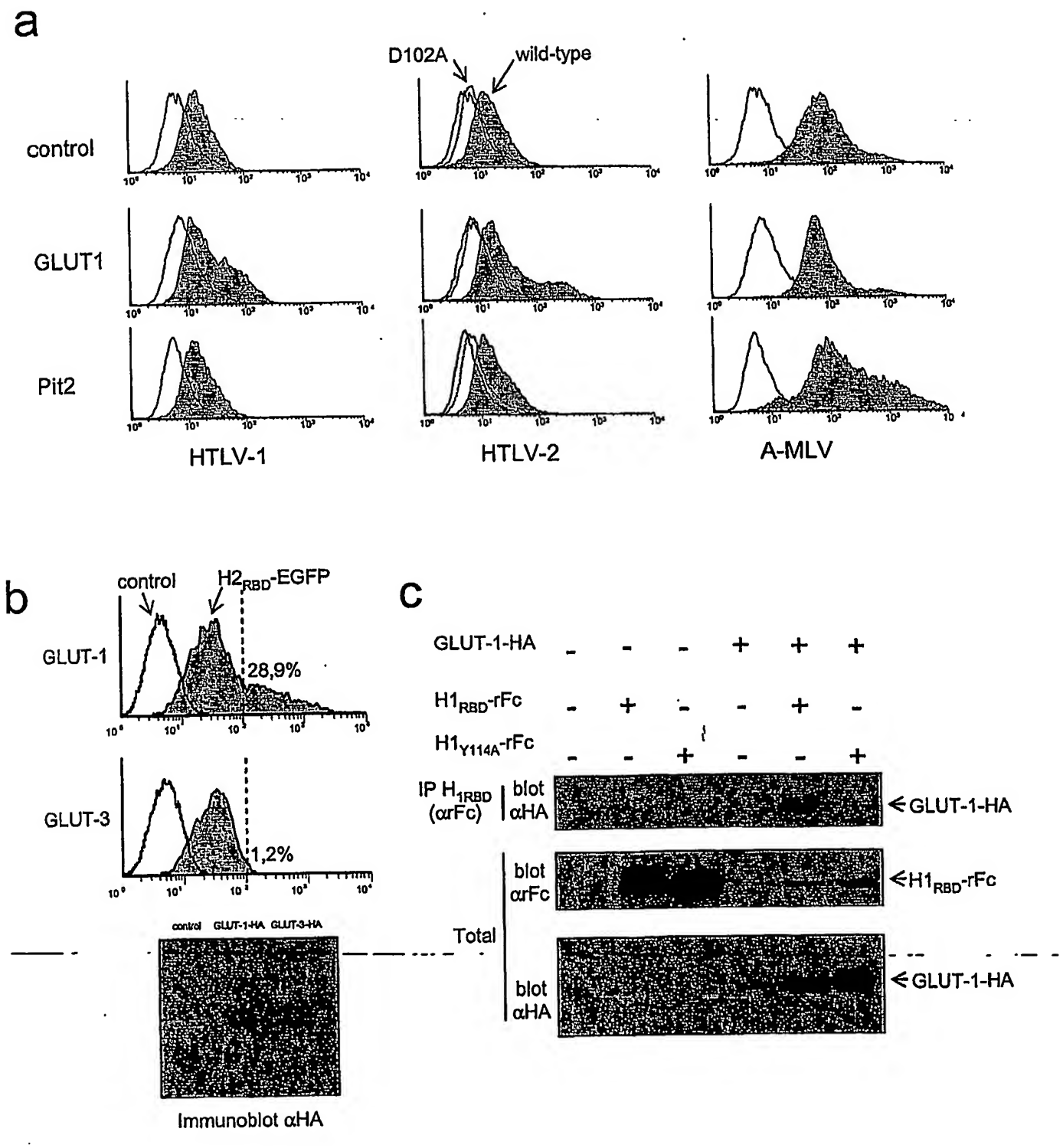
Figure 3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H1Y114A-rFc
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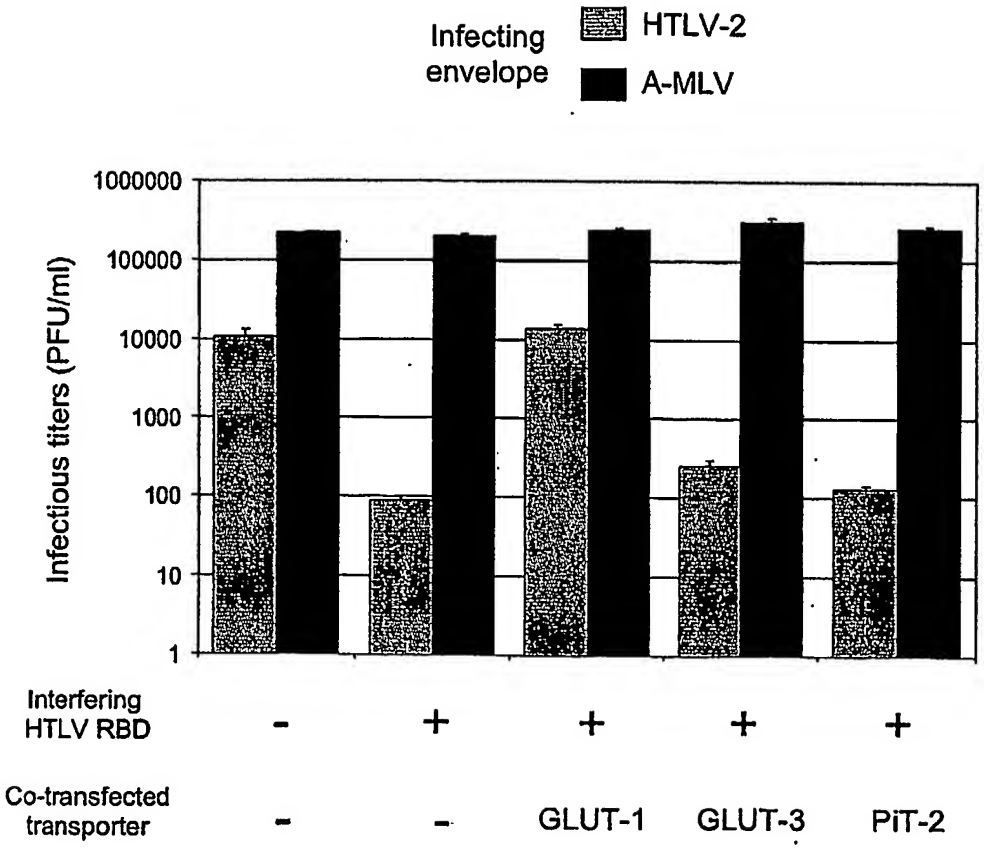
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10000
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- + + + +
Co-transfected transporter
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Figure 5

SEQUENCE LISTING

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Gln Pro Val Tyr Ala Thr Ile Gly Ser Gly Ile Val Asn Thr Ala Phe
305                 310                 315                 320

act gtc gtg tcg ctg ttt gtg gtg gag cga gca ggc cgg cgg acc ctg     1008
Thr Val Val Ser Leu Phe Val Val Glu Arg Ala Gly Arg Arg Thr Leu
                325                 330                 335

cac ctc ata ggc ctc gct ggc atg gcg ggt tgt gcc ata ctc atg acc     1056
His Leu Ile Gly Leu Ala Gly Met Ala Gly Cys Ala Ile Leu Met Thr
            340                 345                 350

atc gcg cta gca ctg ctg gag cag cta ccc tgg atg tcc tat ctg agc     1104
Ile Ala Leu Ala Leu Leu Glu Gln Leu Pro Trp Met Ser Tyr Leu Ser
        355                 360                 365

atc gtg gcc atc ttt ggc ttt gtg gcc ttc ttt gaa gtg ggt cct ggc     1152
Ile Val Ala Ile Phe Gly Phe Val Ala Phe Phe Glu Val Gly Pro Gly
    370                 375                 380

ccc atc cca tgg ttc atc gtg gct gaa ctc ttc agc cag ggt cca cgt     1200
Pro Ile Pro Trp Phe Ile Val Ala Glu Leu Phe Ser Gln Gly Pro Arg
385                 390                 395                 400
```

```
cca gct gcc att gcc gtt gca ggc ttc tcc aac tgg acc tca aat ttc      1248
Pro Ala Ala Ile Ala Val Ala Gly Phe Ser Asn Trp Thr Ser Asn Phe
                405                 410                 415

att gtg ggc atg tgc ttc cag tat gtg gag caa ctg tgt ggt ccc tac      1296
Ile Val Gly Met Cys Phe Gln Tyr Val Glu Gln Leu Cys Gly Pro Tyr
            420                 425                 430

gtc ttc atc atc ttc act gtg ctc ctg gtt ctg ttc ttc atc ttc acc      1344
Val Phe Ile Ile Phe Thr Val Leu Leu Val Leu Phe Phe Ile Phe Thr
        435                 440                 445

tac ttc aaa gtt cct gag act aaa ggc cgg acc ttc gat gag atc gct      1392
Tyr Phe Lys Val Pro Glu Thr Lys Gly Arg Thr Phe Asp Glu Ile Ala
    450                 455                 460

tcc ggc ttc cgg cag ggg gga gcc agc caa agt gat aag aca ccc gag      1440
Ser Gly Phe Arg Gln Gly Gly Ala Ser Gln Ser Asp Lys Thr Pro Glu
465                 470                 475                 480

gag ctg ttc cat ccc ctg ggg gct gat tcc caa gtg tga                  1479
Glu Leu Phe His Pro Leu Gly Ala Asp Ser Gln Val
                485                 490
```

<210> 2
<211> 492
<212> PRT
<213> Homo sapiens

<400> 2

```
Met Glu Pro Ser Ser Lys Lys Leu Thr Gly Arg Leu Met Leu Ala Val
1               5                   10                  15

Gly Gly Ala Val Leu Gly Ser Leu Gln Phe Gly Tyr Asn Thr Gly Val
            20                  25                  30

Ile Asn Ala Pro Gln Lys Val Ile Glu Glu Phe Tyr Asn Gln Thr Trp
        35                  40                  45

Val His Arg Tyr Gly Glu Ser Ile Leu Pro Thr Thr Leu Thr Thr Leu
    50                  55                  60

Trp Ser Leu Ser Val Ala Ile Phe Ser Val Gly Gly Met Ile Gly Ser
65                  70                  75                  80

Phe Ser Val Gly Leu Phe Val Asn Arg Phe Gly Arg Arg Asn Ser Met
                85                  90                  95

Leu Met Met Asn Leu Leu Ala Phe Val Ser Ala Val Leu Met Gly Phe
            100                 105                 110
```

```
Ser Lys Leu Gly Lys Ser Phe Glu Met Leu Ile Leu Gly Arg Phe Ile
        115                 120                 125

Ile Gly Val Tyr Cys Gly Leu Thr Thr Gly Phe Val Pro Met Tyr Val
    130                 135                 140

Gly Glu Val Ser Pro Thr Ala Phe Arg Gly Ala Leu Gly Thr Leu His
145                 150                 155                 160

Gln Leu Gly Ile Val Val Gly Ile Leu Ile Ala Gln Val Phe Gly Leu
                165                 170                 175

Asp Ser Ile Met Gly Asn Lys Asp Leu Trp Pro Leu Leu Leu Ser Ile
            180                 185                 190

Ile Phe Ile Pro Ala Leu Leu Gln Cys Ile Val Leu Pro Phe Cys Pro
        195                 200                 205

Glu Ser Pro Arg Phe Leu Leu Ile Asn Arg Asn Glu Glu Asn Arg Ala
    210                 215                 220

Lys Ser Val Leu Lys Lys Leu Arg Gly Thr Ala Asp Val Thr His Asp
225                 230                 235                 240

Leu Gln Glu Met Lys Glu Glu Ser Arg Gln Met Met Arg Glu Lys Lys
                245                 250                 255

Val Thr Ile Leu Glu Leu Phe Arg Ser Pro Ala Tyr Arg Gln Pro Ile
            260                 265                 270

Leu Ile Ala Val Val Leu Gln Leu Ser Gln Gln Leu Ser Gly Ile Asn
        275                 280                 285

Ala Val Phe Tyr Tyr Ser Thr Ser Ile Phe Glu Lys Ala Gly Val Gln
    290                 295                 300

Gln Pro Val Tyr Ala Thr Ile Gly Ser Gly Ile Val Asn Thr Ala Phe
305                 310                 315                 320

Thr Val Val Ser Leu Phe Val Val Glu Arg Ala Gly Arg Arg Thr Leu
                325                 330                 335

His Leu Ile Gly Leu Ala Gly Met Ala Gly Cys Ala Ile Leu Met Thr
            340                 345                 350

Ile Ala Leu Ala Leu Leu Glu Gln Leu Pro Trp Met Ser Tyr Leu Ser
```

355 360 365

Ile Val Ala Ile Phe Gly Phe Val Ala Phe Phe Glu Val Gly Pro Gly
370 375 380

Pro Ile Pro Trp Phe Ile Val Ala Glu Leu Phe Ser Gln Gly Pro Arg
385 390 395 400

Pro Ala Ala Ile Ala Val Ala Gly Phe Ser Asn Trp Thr Ser Asn Phe
405 410 415

Ile Val Gly Met Cys Phe Gln Tyr Val Glu Gln Leu Cys Gly Pro Tyr
420 425 430

Val Phe Ile Ile Phe Thr Val Leu Leu Val Leu Phe Phe Ile Phe Thr
435 440 445

Tyr Phe Lys Val Pro Glu Thr Lys Gly Arg Thr Phe Asp Glu Ile Ala
450 455 460

Ser Gly Phe Arg Gln Gly Gly Ala Ser Gln Ser Asp Lys Thr Pro Glu
465 470 475 480

Glu Leu Phe His Pro Leu Gly Ala Asp Ser Gln Val
485 490

<210> 3
<211> 924
<212> DNA
<213> Human T-cell lymphotropic virus type 1

<220>
<221> CDS
<222> (1)..(924)
<223>

<400> 3

```
atg ggt aag ttt ctc gcc act ttg att tta ttc ttc cag ttc tgc ccc      48
Met Gly Lys Phe Leu Ala Thr Leu Ile Leu Phe Phe Gln Phe Cys Pro
1               5                  10                  15

ctc atc ctc ggt gat tac agc ccc agc tgc tgt act ctc aca att gga      96
Leu Ile Leu Gly Asp Tyr Ser Pro Ser Cys Cys Thr Leu Thr Ile Gly
            20                  25                  30

gtc tcc tca tac cac tct aaa ccc tgc aat cct gcc cag cca gtt tgt     144
Val Ser Ser Tyr His Ser Lys Pro Cys Asn Pro Ala Gln Pro Val Cys
        35                  40                  45

tcg tgg acc ctc gac ctg ctg gcc ctt tca gcg gat cag gcc cta cag     192
Ser Trp Thr Leu Asp Leu Leu Ala Leu Ser Ala Asp Gln Ala Leu Gln
    50                  55                  60
```

```
ccc ccc tgc cct aat cta gta agt tac tcc agc tac cat gcc acc tat      240
Pro Pro Cys Pro Asn Leu Val Ser Tyr Ser Ser Tyr His Ala Thr Tyr
65                  70                  75                  80

tcc cta tat cta ttc cct cat tgg att aaa aag cca aac cga aat ggc      288
Ser Leu Tyr Leu Phe Pro His Trp Ile Lys Lys Pro Asn Arg Asn Gly
                85                  90                  95

gga ggc tat tat tca gcc tct tat tca gac cct tgt tcc tta aag tgc      336
Gly Gly Tyr Tyr Ser Ala Ser Tyr Ser Asp Pro Cys Ser Leu Lys Cys
            100                 105                 110

cca tac ctg ggg tgc caa tca tgg acc tgc ccc tat aca gga gcc gtc      384
Pro Tyr Leu Gly Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Ala Val
        115                 120                 125

tcc agc ccc tac tgg aag ttt cag caa gat gtc aat ttt act caa gaa      432
Ser Ser Pro Tyr Trp Lys Phe Gln Gln Asp Val Asn Phe Thr Gln Glu
    130                 135                 140

gtt tca cgc ctc aat att aat ctc cat ttt tca aaa tgc ggt ttt ccc      480
Val Ser Arg Leu Asn Ile Asn Leu His Phe Ser Lys Cys Gly Phe Pro
145                 150                 155                 160

ttc tcc ctt cta gtc gac gct cca gga tat gac ccc atc tgg ttc ctt      528
Phe Ser Leu Leu Val Asp Ala Pro Gly Tyr Asp Pro Ile Trp Phe Leu
                165                 170                 175

aat acc gaa ccc agc caa ctg cct ccc acc gcc cct cct cta ctc ccc      576
Asn Thr Glu Pro Ser Gln Leu Pro Pro Thr Ala Pro Pro Leu Leu Pro
            180                 185                 190

cac tct aac cta gac cac atc ctc gag ccc tct ata cca tgg aaa tca      624
His Ser Asn Leu Asp His Ile Leu Glu Pro Ser Ile Pro Trp Lys Ser
        195                 200                 205

aaa ctc ctg acc ctt gtc cag tta acc cta caa agc act aat tat act      672
Lys Leu Leu Thr Leu Val Gln Leu Thr Leu Gln Ser Thr Asn Tyr Thr
    210                 215                 220

tgc att gtc tgt atc gat cgt gcc agc cta tcc act tgg cac gtc cta      720
Cys Ile Val Cys Ile Asp Arg Ala Ser Leu Ser Thr Trp His Val Leu
225                 230                 235                 240

tac tct ccc aac gtc tct gtt cca tcc tct tct tct acc ccc ctc ctt      768
Tyr Ser Pro Asn Val Ser Val Pro Ser Ser Ser Ser Thr Pro Leu Leu
                245                 250                 255

tac cca tcg tta gcg ctt cca gcc ccc cac ctg acg tta cca ttt aac      816
Tyr Pro Ser Leu Ala Leu Pro Ala Pro His Leu Thr Leu Pro Phe Asn
            260                 265                 270

tgg acc cac tgc ttt gac ccc cag att caa gct ata gtc tcc tcc ccc      864
Trp Thr His Cys Phe Asp Pro Gln Ile Gln Ala Ile Val Ser Ser Pro
        275                 280                 285

tgt cat aac tcc ctc atc ctg ccc ccc ttt tcc ttg tca cct gtt ccc      912
Cys His Asn Ser Leu Ile Leu Pro Pro Phe Ser Leu Ser Pro Val Pro
    290                 295                 300
```

acc cta gga tcc
Thr Leu Gly Ser
305 924

<210> 4
<211> 308
<212> PRT
<213> Human T-cell lymphotropic virus type 1

<400> 4

Met Gly Lys Phe Leu Ala Thr Leu Ile Leu Phe Phe Gln Phe Cys Pro
1 5 10 15

Leu Ile Leu Gly Asp Tyr Ser Pro Ser Cys Cys Thr Leu Thr Ile Gly
20 25 30

Val Ser Ser Tyr His Ser Lys Pro Cys Asn Pro Ala Gln Pro Val Cys
35 40 45

Ser Trp Thr Leu Asp Leu Leu Ala Leu Ser Ala Asp Gln Ala Leu Gln
50 55 60

Pro Pro Cys Pro Asn Leu Val Ser Tyr Ser Ser Tyr His Ala Thr Tyr
65 70 75 80

Ser Leu Tyr Leu Phe Pro His Trp Ile Lys Lys Pro Asn Arg Asn Gly
85 90 95

Gly Gly Tyr Tyr Ser Ala Ser Tyr Ser Asp Pro Cys Ser Leu Lys Cys
100 105 110

Pro Tyr Leu Gly Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Ala Val
115 120 125

Ser Ser Pro Tyr Trp Lys Phe Gln Gln Asp Val Asn Phe Thr Gln Glu
130 135 140

Val Ser Arg Leu Asn Ile Asn Leu His Phe Ser Lys Cys Gly Phe Pro
145 150 155 160

Phe Ser Leu Leu Val Asp Ala Pro Gly Tyr Asp Pro Ile Trp Phe Leu
165 170 175

Asn Thr Glu Pro Ser Gln Leu Pro Pro Thr Ala Pro Pro Leu Leu Pro
180 185 190

His Ser Asn Leu Asp His Ile Leu Glu Pro Ser Ile Pro Trp Lys Ser

```
        195                 200                 205

Lys Leu Leu Thr Leu Val Gln Leu Thr Leu Gln Ser Thr Asn Tyr Thr
    210                 215                 220

Cys Ile Val Cys Ile Asp Arg Ala Ser Leu Ser Thr Trp His Val Leu
225                 230                 235                 240

Tyr Ser Pro Asn Val Ser Val Pro Ser Ser Ser Ser Thr Pro Leu Leu
                245                 250                 255

Tyr Pro Ser Leu Ala Leu Pro Ala Pro His Leu Thr Leu Pro Phe Asn
            260                 265                 270

Trp Thr His Cys Phe Asp Pro Gln Ile Gln Ala Ile Val Ser Ser Pro
        275                 280                 285

Cys His Asn Ser Leu Ile Leu Pro Pro Phe Ser Leu Ser Pro Val Pro
    290                 295                 300

Thr Leu Gly Ser
305


<210>  5
<211>  912
<212>  DNA
<213>  Human T-cell lymphotropic virus type 2

<220>
<221>  CDS
<222>  (1)..(912)
<223>

<400>  5
atg ggt aac gtt ttc ttc cta ctt tta ttc agt ctc aca cac ttc cca       48
Met Gly Asn Val Phe Phe Leu Leu Leu Phe Ser Leu Thr His Phe Pro
1               5                   10                  15

cca gtc cag cag agc cga tgc aca ctc acg gtt ggt att tcc tcc tac       96
Pro Val Gln Gln Ser Arg Cys Thr Leu Thr Val Gly Ile Ser Ser Tyr
            20                  25                  30

cac tcc agc ccc tgt agc cca acc caa ccc gtc tgc acg tgg aac ctc      144
His Ser Ser Pro Cys Ser Pro Thr Gln Pro Val Cys Thr Trp Asn Leu
        35                  40                  45

gac ctt aat tcc cta acg acg gac cag cga cta cat ccc ccc tgc cct      192
Asp Leu Asn Ser Leu Thr Thr Asp Gln Arg Leu His Pro Pro Cys Pro
    50                  55                  60

aac cta att act tac tct ggc ttc cac aaa act tat tcc tta tac tta      240
Asn Leu Ile Thr Tyr Ser Gly Phe His Lys Thr Tyr Ser Leu Tyr Leu
65                  70                  75                  80
```

```
ttc cca cat tgg ata aag aag cca aat aga cag ggc cta gga tac tac      288
Phe Pro His Trp Ile Lys Lys Pro Asn Arg Gln Gly Leu Gly Tyr Tyr
                85                  90                  95

tcg ccc tcc tat aat gac cct tgc tcg cta caa tgc ccc tac tta ggc      336
Ser Pro Ser Tyr Asn Asp Pro Cys Ser Leu Gln Cys Pro Tyr Leu Gly
            100                 105                 110

tgc caa tca tgg aca tgc cca tac acg ggc ccc gtc tcc agt cca tcc      384
Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Pro Val Ser Ser Pro Ser
        115                 120                 125

tgg aag ttt cac tca gat gta aat ttc acc caa gaa gtc agc caa gtg      432
Trp Lys Phe His Ser Asp Val Asn Phe Thr Gln Glu Val Ser Gln Val
    130                 135                 140

tcc ctt cga cta cac ttc tct aag tgc ggc tcc tcc atg acc ctt cta      480
Ser Leu Arg Leu His Phe Ser Lys Cys Gly Ser Ser Met Thr Leu Leu
145                 150                 155                 160

gta gat gcc cct gga tat gat cct tta tgg ttc atc acc tca gaa ccc      528
Val Asp Ala Pro Gly Tyr Asp Pro Leu Trp Phe Ile Thr Ser Glu Pro
                165                 170                 175

act cag cct ccc cca act cct ccc cca ctg gtc cat gac tcc gac ctt      576
Thr Gln Pro Pro Pro Thr Pro Pro Pro Leu Val His Asp Ser Asp Leu
            180                 185                 190

gaa cac gtc cta acc ccc tcc acg tct tgg aca acc aaa atg ctc aag      624
Glu His Val Leu Thr Pro Ser Thr Ser Trp Thr Thr Lys Met Leu Lys
        195                 200                 205

ttt atc cag ctg acc ttg cag agc acc aat tac tcc tgc atg gtt tgc      672
Phe Ile Gln Leu Thr Leu Gln Ser Thr Asn Tyr Ser Cys Met Val Cys
    210                 215                 220

gtg gat aga tcc agc ctc tca tcc tgg cat gtg ctc tac acc ccc aac      720
Val Asp Arg Ser Ser Leu Ser Ser Trp His Val Leu Tyr Thr Pro Asn
225                 230                 235                 240

atc tcc att ccc caa caa acc tcc tcc cga acc atc ctc ttt cct tct      768
Ile Ser Ile Pro Gln Gln Thr Ser Ser Arg Thr Ile Leu Phe Pro Ser
                245                 250                 255

ctt gcc ctg ccc gct cct cca ttc caa ccc ttc cct tgg acc cat tgc      816
Leu Ala Leu Pro Ala Pro Pro Phe Gln Pro Phe Pro Trp Thr His Cys
            260                 265                 270

tac caa cct cgc cta cag gca ata acg aca gat gac tgc aac aac tcc      864
Tyr Gln Pro Arg Leu Gln Ala Ile Thr Thr Asp Asp Cys Asn Asn Ser
        275                 280                 285

att atc ctc ccc cct ttt tcc ctc gcc ccc gta cct cct ccg gcg aca      912
Ile Ile Leu Pro Pro Phe Ser Leu Ala Pro Val Pro Pro Pro Ala Thr
    290                 295                 300
```

<210> 6
<211> 304
<212> PRT

<213> Human T-cell lymphotropic virus type 2

<400> 6

Met Gly Asn Val Phe Phe Leu Leu Leu Phe Ser Leu Thr His Phe Pro
1 5 10 15

Pro Val Gln Gln Ser Arg Cys Thr Leu Thr Val Gly Ile Ser Ser Tyr
20 25 30

His Ser Ser Pro Cys Ser Pro Thr Gln Pro Val Cys Thr Trp Asn Leu
35 40 45

Asp Leu Asn Ser Leu Thr Thr Asp Gln Arg Leu His Pro Pro Cys Pro
50 55 60

Asn Leu Ile Thr Tyr Ser Gly Phe His Lys Thr Tyr Ser Leu Tyr Leu
65 70 75 80

Phe Pro His Trp Ile Lys Lys Pro Asn Arg Gln Gly Leu Gly Tyr Tyr
85 90 95

Ser Pro Ser Tyr Asn Asp Pro Cys Ser Leu Gln Cys Pro Tyr Leu Gly
100 105 110

Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Pro Val Ser Ser Pro Ser
115 120 125

Trp Lys Phe His Ser Asp Val Asn Phe Thr Gln Glu Val Ser Gln Val
130 135 140

Ser Leu Arg Leu His Phe Ser Lys Cys Gly Ser Ser Met Thr Leu Leu
145 150 155 160

Val Asp Ala Pro Gly Tyr Asp Pro Leu Trp Phe Ile Thr Ser Glu Pro
165 170 175

Thr Gln Pro Pro Pro Thr Pro Pro Pro Leu Val His Asp Ser Asp Leu
180 185 190

Glu His Val Leu Thr Pro Ser Thr Ser Trp Thr Thr Lys Met Leu Lys
195 200 205

Phe Ile Gln Leu Thr Leu Gln Ser Thr Asn Tyr Ser Cys Met Val Cys
210 215 220

Val Asp Arg Ser Ser Leu Ser Ser Trp His Val Leu Tyr Thr Pro Asn

```
225                 230                 235                 240

Ile Ser Ile Pro Gln Gln Thr Ser Ser Arg Thr Ile Leu Phe Pro Ser
                245                 250                 255

Leu Ala Leu Pro Ala Pro Pro Phe Gln Pro Phe Pro Trp Thr His Cys
            260                 265                 270

Tyr Gln Pro Arg Leu Gln Ala Ile Thr Thr Asp Asp Cys Asn Asn Ser
        275                 280                 285

Ile Ile Leu Pro Pro Phe Ser Leu Ala Pro Val Pro Pro Pro Ala Thr
    290                 295                 300
```

<210> 7
<211> 1467
<212> DNA
<213> Simian T-cell lymphotropic virus type 1

<220>
<221> CDS
<222> (1)..(1467)
<223>

<400> 7

```
atg ggt aag ttt ctc gcc act ttg att tta ttc ttc cag ttc tgc ccc      48
Met Gly Lys Phe Leu Ala Thr Leu Ile Leu Phe Phe Gln Phe Cys Pro
1               5                   10                  15

ctc att ctc ggt gat tac agc ccc agc tgc tgt act ctc aca att gga      96
Leu Ile Leu Gly Asp Tyr Ser Pro Ser Cys Cys Thr Leu Thr Ile Gly
            20                  25                  30

gtc tcc tca tac ctc tct aaa ccc tgc aat cct gcc cag cca gtt tgt     144
Val Ser Ser Tyr Leu Ser Lys Pro Cys Asn Pro Ala Gln Pro Val Cys
        35                  40                  45

tca tgg acc ctc gac cta ctg gcc ctt tca gca gac caa gcc cta cag     192
Ser Trp Thr Leu Asp Leu Leu Ala Leu Ser Ala Asp Gln Ala Leu Gln
    50                  55                  60

ccc ccc tgc cct aat cta gta agt tac tcc agc tac cat gcc acc tat     240
Pro Pro Cys Pro Asn Leu Val Ser Tyr Ser Ser Tyr His Ala Thr Tyr
65                  70                  75                  80

tcc cta tat cta ttc cct cat tgg att aaa aag cca aac cga aat ggc     288
Ser Leu Tyr Leu Phe Pro His Trp Ile Lys Lys Pro Asn Arg Asn Gly
                85                  90                  95

gga ggc tat tat tcg gcc tct tat tca gac cca tgt tct tta aag tgc     336
Gly Gly Tyr Tyr Ser Ala Ser Tyr Ser Asp Pro Cys Ser Leu Lys Cys
            100                 105                 110

cca tac tta ggg tgc caa tca tgg acc tgc ccc tat aca gga gtc gtc     384
Pro Tyr Leu Gly Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Val Val
        115                 120                 125
```

```
tcc agc ccc tat tgg aaa ttt cag caa gat gtc aat ttt act caa gaa      432
Ser Ser Pro Tyr Trp Lys Phe Gln Gln Asp Val Asn Phe Thr Gln Glu
    130                 135                 140

gtt tca cac ctc aat att aat ctc cat ttc tca aaa tgc ggt ttt ccc      480
Val Ser His Leu Asn Ile Asn Leu His Phe Ser Lys Cys Gly Phe Pro
145                 150                 155                 160

ttc tcc ctt cta atc gac gct cca gga tat gac ccc atc tgg ttc ctt      528
Phe Ser Leu Leu Ile Asp Ala Pro Gly Tyr Asp Pro Ile Trp Phe Leu
                165                 170                 175

aat acc gaa ccc agc caa ctg cct ccc acc gcc cct cct cta ctc ccc      576
Asn Thr Glu Pro Ser Gln Leu Pro Pro Thr Ala Pro Pro Leu Leu Pro
            180                 185                 190

cac tct aac ctg gac cac atc ctc gag ccc tct ata cca tgg aaa tca      624
His Ser Asn Leu Asp His Ile Leu Glu Pro Ser Ile Pro Trp Lys Ser
        195                 200                 205

aaa ctt ctg act ctt gtc cag cta acc cta caa agc act aat tac act      672
Lys Leu Leu Thr Leu Val Gln Leu Thr Leu Gln Ser Thr Asn Tyr Thr
    210                 215                 220

tgc atc gtc tgt ata gac cgt gcc agc ctc tct act tgg cat gtc ctg      720
Cys Ile Val Cys Ile Asp Arg Ala Ser Leu Ser Thr Trp His Val Leu
225                 230                 235                 240

tac tct ccc aac gtc tct gtt ccg tcc tct tct tct acc ccc ctc ctt      768
Tyr Ser Pro Asn Val Ser Val Pro Ser Ser Ser Ser Thr Pro Leu Leu
                245                 250                 255

tac ccg tcg tta gcg ctt cca gct ccc cac ctg acg cta cca ttt aac      816
Tyr Pro Ser Leu Ala Leu Pro Ala Pro His Leu Thr Leu Pro Phe Asn
            260                 265                 270

tgg acc cac tgc ttt gac ccc cag att caa gct ata gtc tcc tcc ccc      864
Trp Thr His Cys Phe Asp Pro Gln Ile Gln Ala Ile Val Ser Ser Pro
        275                 280                 285

tgt cat aac tcc ctc atc ctg ccc ccc ttt tcc ttg tca cct gtt ccc      912
Cys His Asn Ser Leu Ile Leu Pro Pro Phe Ser Leu Ser Pro Val Pro
    290                 295                 300

acc cta gga tcc cgc tcc cgc cga gcg gta ccg gtg gcg gtc tgg ctt      960
Thr Leu Gly Ser Arg Ser Arg Arg Ala Val Pro Val Ala Val Trp Leu
305                 310                 315                 320

gtc tcc gcc ctg gcc atg gga gcc gga att gct ggc ggg att acc ggc     1008
Val Ser Ala Leu Ala Met Gly Ala Gly Ile Ala Gly Gly Ile Thr Gly
                325                 330                 335

tcc atg tcc ctc gcc tca gga aag agc ctc cta cat gag gtg gac aaa     1056
Ser Met Ser Leu Ala Ser Gly Lys Ser Leu Leu His Glu Val Asp Lys
            340                 345                 350

gat att tcc caa tta act caa gca ata gtc aaa aac cac aaa aat cta     1104
Asp Ile Ser Gln Leu Thr Gln Ala Ile Val Lys Asn His Lys Asn Leu
        355                 360                 365
```

```
ctc aaa att gca cag tat gct gcc cag aac agg cga ggc ctt gat ctc      1152
Leu Lys Ile Ala Gln Tyr Ala Ala Gln Asn Arg Arg Gly Leu Asp Leu
    370                 375                 380

ctg ttc tgg gag caa gga gga tta tgc aaa gca tta caa gaa cag tgc      1200
Leu Phe Trp Glu Gln Gly Gly Leu Cys Lys Ala Leu Gln Glu Gln Cys
385                 390                 395                 400

tgt ttt cta aat att acc aat tcc cat gtc tca ata cta caa gaa aga      1248
Cys Phe Leu Asn Ile Thr Asn Ser His Val Ser Ile Leu Gln Glu Arg
                405                 410                 415

ccc ccc ctt gag aat cga gtc ctc act ggc tgg ggc ctt aac tgg gac      1296
Pro Pro Leu Glu Asn Arg Val Leu Thr Gly Trp Gly Leu Asn Trp Asp
            420                 425                 430

ctt ggc ctc tca cag tgg gct cga gag gcc tta caa act ggg atc acc      1344
Leu Gly Leu Ser Gln Trp Ala Arg Glu Ala Leu Gln Thr Gly Ile Thr
        435                 440                 445

ctt gtt gca cta ctc ctt ctc gtt atc ctt gca gga cca tgc atc ctc      1392
Leu Val Ala Leu Leu Leu Leu Val Ile Leu Ala Gly Pro Cys Ile Leu
    450                 455                 460

cgt cag ctg cga cac ctc ccc tcg cgc gtc aga tac ccc cat tat tct      1440
Arg Gln Leu Arg His Leu Pro Ser Arg Val Arg Tyr Pro His Tyr Ser
465                 470                 475                 480

ctt ata aac cct gag tca tcc ctg taa                                  1467
Leu Ile Asn Pro Glu Ser Ser Leu
                485
```

<210> 8
<211> 488
<212> PRT
<213> Simian T-cell lymphotropic virus type 1

<400> 8

```
Met Gly Lys Phe Leu Ala Thr Leu Ile Leu Phe Phe Gln Phe Cys Pro
1               5                   10                  15

Leu Ile Leu Gly Asp Tyr Ser Pro Ser Cys Cys Thr Leu Thr Ile Gly
            20                  25                  30

Val Ser Ser Tyr Leu Ser Lys Pro Cys Asn Pro Ala Gln Pro Val Cys
        35                  40                  45

Ser Trp Thr Leu Asp Leu Leu Ala Leu Ser Ala Asp Gln Ala Leu Gln
    50                  55                  60

Pro Pro Cys Pro Asn Leu Val Ser Tyr Ser Ser Tyr His Ala Thr Tyr
65                  70                  75                  80

Ser Leu Tyr Leu Phe Pro His Trp Ile Lys Lys Pro Asn Arg Asn Gly
```

```
                85                  90                  95

Gly Gly Tyr Tyr Ser Ala Ser Tyr Ser Asp Pro Cys Ser Leu Lys Cys
            100                 105                 110

Pro Tyr Leu Gly Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Val Val
        115                 120                 125

Ser Ser Pro Tyr Trp Lys Phe Gln Gln Asp Val Asn Phe Thr Gln Glu
    130                 135                 140

Val Ser His Leu Asn Ile Asn Leu His Phe Ser Lys Cys Gly Phe Pro
145                 150                 155                 160

Phe Ser Leu Leu Ile Asp Ala Pro Gly Tyr Asp Pro Ile Trp Phe Leu
                165                 170                 175

Asn Thr Glu Pro Ser Gln Leu Pro Pro Thr Ala Pro Pro Leu Leu Pro
            180                 185                 190

His Ser Asn Leu Asp His Ile Leu Glu Pro Ser Ile Pro Trp Lys Ser
        195                 200                 205

Lys Leu Leu Thr Leu Val Gln Leu Thr Leu Gln Ser Thr Asn Tyr Thr
    210                 215                 220

Cys Ile Val Cys Ile Asp Arg Ala Ser Leu Ser Thr Trp His Val Leu
225                 230                 235                 240

Tyr Ser Pro Asn Val Ser Val Pro Ser Ser Ser Ser Thr Pro Leu Leu
                245                 250                 255

Tyr Pro Ser Leu Ala Leu Pro Ala Pro His Leu Thr Leu Pro Phe Asn
            260                 265                 270

Trp Thr His Cys Phe Asp Pro Gln Ile Gln Ala Ile Val Ser Ser Pro
        275                 280                 285

Cys His Asn Ser Leu Ile Leu Pro Pro Phe Ser Leu Ser Pro Val Pro
    290                 295                 300

Thr Leu Gly Ser Arg Ser Arg Arg Ala Val Pro Val Ala Val Trp Leu
305                 310                 315                 320

Val Ser Ala Leu Ala Met Gly Ala Gly Ile Ala Gly Gly Ile Thr Gly
                325                 330                 335
```

Ser Met Ser Leu Ala Ser Gly Lys Ser Leu Leu His Glu Val Asp Lys
340 345 350

Asp Ile Ser Gln Leu Thr Gln Ala Ile Val Lys Asn His Lys Asn Leu
355 360 365

Leu Lys Ile Ala Gln Tyr Ala Ala Gln Asn Arg Arg Gly Leu Asp Leu
370 375 380

Leu Phe Trp Glu Gln Gly Gly Leu Cys Lys Ala Leu Gln Glu Gln Cys
385 390 395 400

Cys Phe Leu Asn Ile Thr Asn Ser His Val Ser Ile Leu Gln Glu Arg
405 410 415

Pro Pro Leu Glu Asn Arg Val Leu Thr Gly Trp Gly Leu Asn Trp Asp
420 425 430

Leu Gly Leu Ser Gln Trp Ala Arg Glu Ala Leu Gln Thr Gly Ile Thr
435 440 445

Leu Val Ala Leu Leu Leu Leu Val Ile Leu Ala Gly Pro Cys Ile Leu
450 455 460

Arg Gln Leu Arg His Leu Pro Ser Arg Val Arg Tyr Pro His Tyr Ser
465 470 475 480

Leu Ile Asn Pro Glu Ser Ser Leu
485

<210> 9
<211> 1461
<212> DNA
<213> Simian T-cell lymphotropic virus type 2

<220>
<221> CDS
<222> (1)..(1461)
<223>

<400> 9
atg ggt aag ata att gct ttc ctt tta ttc cat ctt aca tgt atc aca 48
Met Gly Lys Ile Ile Ala Phe Leu Leu Phe His Leu Thr Cys Ile Thr
1 5 10 15

atc act aaa cag agc cgg tgc acg ctt acg gta ggt gtc tcc tcg tat 96
Ile Thr Lys Gln Ser Arg Cys Thr Leu Thr Val Gly Val Ser Ser Tyr
20 25 30

```
cac tct agt ccc tgc agt ctt gcc caa cct atc tgc acc tgg gat ctc      144
His Ser Ser Pro Cys Ser Leu Ala Gln Pro Ile Cys Thr Trp Asp Leu
        35                  40                  45

gac ctt cat tcc tta act aca gac caa cgt ctg tac cct cca tgc ccc      192
Asp Leu His Ser Leu Thr Thr Asp Gln Arg Leu Tyr Pro Pro Cys Pro
    50                  55                  60

aat cta gtt tct tac tct aac ttc cac aag tcc tac tcc tta tat ttg      240
Asn Leu Val Ser Tyr Ser Asn Phe His Lys Ser Tyr Ser Leu Tyr Leu
65                  70                  75                  80

ttc ccg cac tgg gta aaa aag cca aat aga caa ggc ctg gga tac tat      288
Phe Pro His Trp Val Lys Lys Pro Asn Arg Gln Gly Leu Gly Tyr Tyr
                85                  90                  95

tct gca tcc tac agc gac ccc tgc tcg ctc cag tgc cct tat tta gga      336
Ser Ala Ser Tyr Ser Asp Pro Cys Ser Leu Gln Cys Pro Tyr Leu Gly
            100                 105                 110

agc cag tct tgg aca tgc cct tac acc ggc ccc atc tcc agc ccg tct      384
Ser Gln Ser Trp Thr Cys Pro Tyr Thr Gly Pro Ile Ser Ser Pro Ser
        115                 120                 125

tgg agg ttc cac cga gat gtt aac ttc acc caa gag gtc aac cat gta      432
Trp Arg Phe His Arg Asp Val Asn Phe Thr Gln Glu Val Asn His Val
    130                 135                 140

acc ctc cgg cta cac ttc tcc cga tgt ggc tct tct atg acc ctc ctc      480
Thr Leu Arg Leu His Phe Ser Arg Cys Gly Ser Ser Met Thr Leu Leu
145                 150                 155                 160

ata gac gcc cca ggc tac gac ccc ctg tgg ttc atc tct tcg gaa ccc      528
Ile Asp Ala Pro Gly Tyr Asp Pro Leu Trp Phe Ile Ser Ser Glu Pro
                165                 170                 175

act cag ccc ccc ccc act tcc cca cca tta gtc cgc gac tct gac ctt      576
Thr Gln Pro Pro Pro Thr Ser Pro Pro Leu Val Arg Asp Ser Asp Leu
            180                 185                 190

gaa cat atc tta acc ccc tcc tcc tcc tgg gct act agg atg cta acc      624
Glu His Ile Leu Thr Pro Ser Ser Ser Trp Ala Thr Arg Met Leu Thr
        195                 200                 205

ctc atc caa cta act cta caa agt acc aat tat tct tgc atg gtt tgt      672
Leu Ile Gln Leu Thr Leu Gln Ser Thr Asn Tyr Ser Cys Met Val Cys
    210                 215                 220

ata gac aga acc agc ttg tcg tcc tgg cac gta ctc tat acc cct aat      720
Ile Asp Arg Thr Ser Leu Ser Ser Trp His Val Leu Tyr Thr Pro Asn
225                 230                 235                 240

atc tct gcc tca cct ggg ggc gac tcc ttg cct ata ctt tat ccc tcc      768
Ile Ser Ala Ser Pro Gly Gly Asp Ser Leu Pro Ile Leu Tyr Pro Ser
                245                 250                 255

ttg gcc cta ccg gcc ccc caa ccc cag ccg ttt tcc tgg tct cac tgt      816
Leu Ala Leu Pro Ala Pro Gln Pro Gln Pro Phe Ser Trp Ser His Cys
            260                 265                 270

tac cag ccc cac cta cag gca gta act aca gcc aat tgc aac aat tcc      864
```

```
Tyr Gln Pro His Leu Gln Ala Val Thr Thr Ala Asn Cys Asn Asn Ser
        275                 280                 285

att gtc ctg ccc cca ttc tct ctc acc ccg gtg cct tcc cct ggg aca      912
Ile Val Leu Pro Pro Phe Ser Leu Thr Pro Val Pro Ser Pro Gly Thr
    290                 295                 300

aga agc cgc cgg gct att cca gtg gct gta tgg ctc gtc tca gcc cta      960
Arg Ser Arg Arg Ala Ile Pro Val Ala Val Trp Leu Val Ser Ala Leu
305                 310                 315                 320

gcg gcc ggg act ggt att gca ggg gga ata acc gga tcc ctg tcc cta     1008
Ala Ala Gly Thr Gly Ile Ala Gly Gly Ile Thr Gly Ser Leu Ser Leu
                325                 330                 335

gca tca agc cgc agc ctg ctt ttt gaa gtt gac aaa gat att tcc cac     1056
Ala Ser Ser Arg Ser Leu Leu Phe Glu Val Asp Lys Asp Ile Ser His
            340                 345                 350

ctc aca caa gcc atc gtt aaa aac cat caa aac atc ctc cgc gta gca     1104
Leu Thr Gln Ala Ile Val Lys Asn His Gln Asn Ile Leu Arg Val Ala
        355                 360                 365

caa tat gca gcc caa aat aga aga gga cta gac ctc ctg ttt tgg gaa     1152
Gln Tyr Ala Ala Gln Asn Arg Arg Gly Leu Asp Leu Leu Phe Trp Glu
    370                 375                 380

caa gga ggc ctc tgc aaa gcc ata caa gag caa tgt tgc ttc ctt aac     1200
Gln Gly Gly Leu Cys Lys Ala Ile Gln Glu Gln Cys Cys Phe Leu Asn
385                 390                 395                 400

atc agc aac acc cat gtg tcc gtc ctt cag gag cgc ccc ccc ctg gaa     1248
Ile Ser Asn Thr His Val Ser Val Leu Gln Glu Arg Pro Pro Leu Glu
                405                 410                 415

aag aga gtc atc aca gga tgg ggt ctc aac tgg gac cta ggg cta tcc     1296
Lys Arg Val Ile Thr Gly Trp Gly Leu Asn Trp Asp Leu Gly Leu Ser
            420                 425                 430

caa tgg gca cgg gaa gca ctc caa act ggt ata acc atc cta gcc ttg     1344
Gln Trp Ala Arg Glu Ala Leu Gln Thr Gly Ile Thr Ile Leu Ala Leu
        435                 440                 445

ctc ctc ctt gtc ata ctg ttc ggt cct tgt atc ctt cgc caa ctc caa     1392
Leu Leu Leu Val Ile Leu Phe Gly Pro Cys Ile Leu Arg Gln Leu Gln
    450                 455                 460

tca ctt ccc cac cgg cta cag aac agg cac aac caa tac tct ctt att     1440
Ser Leu Pro His Arg Leu Gln Asn Arg His Asn Gln Tyr Ser Leu Ile
465                 470                 475                 480

aac cag gaa acc aca cta taa                                        1461
Asn Gln Glu Thr Thr Leu
                485
```

<210> 10
<211> 486
<212> PRT
<213> Simian T-cell lymphotropic virus type 2

<400> 10

```
Met Gly Lys Ile Ile Ala Phe Leu Leu Phe His Leu Thr Cys Ile Thr
1               5                  10                  15

Ile Thr Lys Gln Ser Arg Cys Thr Leu Thr Val Gly Val Ser Ser Tyr
            20                  25                  30

His Ser Ser Pro Cys Ser Leu Ala Gln Pro Ile Cys Thr Trp Asp Leu
        35                  40                  45

Asp Leu His Ser Leu Thr Thr Asp Gln Arg Leu Tyr Pro Pro Cys Pro
    50                  55                  60

Asn Leu Val Ser Tyr Ser Asn Phe His Lys Ser Tyr Ser Leu Tyr Leu
65                  70                  75                  80

Phe Pro His Trp Val Lys Lys Pro Asn Arg Gln Gly Leu Gly Tyr Tyr
                85                  90                  95

Ser Ala Ser Tyr Ser Asp Pro Cys Ser Leu Gln Cys Pro Tyr Leu Gly
            100                 105                 110

Ser Gln Ser Trp Thr Cys Pro Tyr Thr Gly Pro Ile Ser Ser Pro Ser
        115                 120                 125

Trp Arg Phe His Arg Asp Val Asn Phe Thr Gln Glu Val Asn His Val
    130                 135                 140

Thr Leu Arg Leu His Phe Ser Arg Cys Gly Ser Ser Met Thr Leu Leu
145                 150                 155                 160

Ile Asp Ala Pro Gly Tyr Asp Pro Leu Trp Phe Ile Ser Ser Glu Pro
                165                 170                 175

Thr Gln Pro Pro Pro Thr Ser Pro Pro Leu Val Arg Asp Ser Asp Leu
            180                 185                 190

Glu His Ile Leu Thr Pro Ser Ser Ser Trp Ala Thr Arg Met Leu Thr
        195                 200                 205

Leu Ile Gln Leu Thr Leu Gln Ser Thr Asn Tyr Ser Cys Met Val Cys
    210                 215                 220

Ile Asp Arg Thr Ser Leu Ser Ser Trp His Val Leu Tyr Thr Pro Asn
225                 230                 235                 240
```

```
Ile Ser Ala Ser Pro Gly Gly Asp Ser Leu Pro Ile Leu Tyr Pro Ser
                245                 250                 255

Leu Ala Leu Pro Ala Pro Gln Pro Gln Pro Phe Ser Trp Ser His Cys
            260                 265                 270

Tyr Gln Pro His Leu Gln Ala Val Thr Thr Ala Asn Cys Asn Asn Ser
        275                 280                 285

Ile Val Leu Pro Pro Phe Ser Leu Thr Pro Val Pro Ser Pro Gly Thr
    290                 295                 300

Arg Ser Arg Arg Ala Ile Pro Val Ala Val Trp Leu Val Ser Ala Leu
305                 310                 315                 320

Ala Ala Gly Thr Gly Ile Ala Gly Gly Ile Thr Gly Ser Leu Ser Leu
                325                 330                 335

Ala Ser Ser Arg Ser Leu Leu Phe Glu Val Asp Lys Asp Ile Ser His
            340                 345                 350

Leu Thr Gln Ala Ile Val Lys Asn His Gln Asn Ile Leu Arg Val Ala
        355                 360                 365

Gln Tyr Ala Ala Gln Asn Arg Arg Gly Leu Asp Leu Leu Phe Trp Glu
    370                 375                 380

Gln Gly Gly Leu Cys Lys Ala Ile Gln Glu Gln Cys Cys Phe Leu Asn
385                 390                 395                 400

Ile Ser Asn Thr His Val Ser Val Leu Gln Glu Arg Pro Pro Leu Glu
                405                 410                 415

Lys Arg Val Ile Thr Gly Trp Gly Leu Asn Trp Asp Leu Gly Leu Ser
            420                 425                 430

Gln Trp Ala Arg Glu Ala Leu Gln Thr Gly Ile Thr Ile Leu Ala Leu
        435                 440                 445

Leu Leu Leu Val Ile Leu Phe Gly Pro Cys Ile Leu Arg Gln Leu Gln
    450                 455                 460

Ser Leu Pro His Arg Leu Gln Asn Arg His Asn Gln Tyr Ser Leu Ile
465                 470                 475                 480
```

Asn Gln Glu Thr Thr Leu
485

<210> 11
<211> 930
<212> DNA
<213> Simian T-cell lymphotropic virus type 3

<220>
<221> CDS
<222> (1)..(930)
<223>

<400> 11

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atg ggt aag ttt ggc ctt tat tgt ctt gtt cac ctt tac ata ctt ctc       48
Met Gly Lys Phe Gly Leu Tyr Cys Leu Val His Leu Tyr Ile Leu Leu
1               5                   10                  15

cct gcc tcc tct ggc aat ccc agt cgg tgc acc ctg ttc ata ggg gcc       96
Pro Ala Ser Ser Gly Asn Pro Ser Arg Cys Thr Leu Phe Ile Gly Ala
            20                  25                  30

tct tcc tac cac tcc agc cct tgc ggg tcc agc ctc cca cgg tgt acc      144
Ser Ser Tyr His Ser Ser Pro Cys Gly Ser Ser Leu Pro Arg Cys Thr
        35                  40                  45

tgg aat ctt gac cta ttc tcc ctc acg aaa gat caa agc cta agc ccc      192
Trp Asn Leu Asp Leu Phe Ser Leu Thr Lys Asp Gln Ser Leu Ser Pro
    50                  55                  60

cca tgt cca gac tta att act tac tca caa tac cac aag ccc tac tcc      240
Pro Cys Pro Asp Leu Ile Thr Tyr Ser Gln Tyr His Lys Pro Tyr Ser
65                  70                  75                  80

ctg tat gta ttc cct cat tgg ata act aaa cct aac cgc cgg ggc tta      288
Leu Tyr Val Phe Pro His Trp Ile Thr Lys Pro Asn Arg Arg Gly Leu
                85                  90                  95

ggt tac tat tcc gct tcc tac tca gac ccc tgt gcc ata cag tgc cct      336
Gly Tyr Tyr Ser Ala Ser Tyr Ser Asp Pro Cys Ala Ile Gln Cys Pro
            100                 105                 110

tac ctg gga tgc cag tcg tgg aca tgc ccc tat acg ggc ccg gtg tcc      384
Tyr Leu Gly Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Pro Val Ser
        115                 120                 125

agt ccg cat tgg aga tac acc tat gat ctt aac ttt acc cag gag gta      432
Ser Pro His Trp Arg Tyr Thr Tyr Asp Leu Asn Phe Thr Gln Glu Val
    130                 135                 140

tca tcc gtc tcc tta cac ttg cat ttc tcc aaa tgc gga tcc tcg ttc      480
Ser Ser Val Ser Leu His Leu His Phe Ser Lys Cys Gly Ser Ser Phe
145                 150                 155                 160

tcc ttt cta cta gac gca cca gga tat gac cca gtg tgg ttc ctc tcc      528
Ser Phe Leu Leu Asp Ala Pro Gly Tyr Asp Pro Val Trp Phe Leu Ser
                165                 170                 175

tcc cag gcc aca cag gct cca ccc aca cct gcc cct ctc ata cgg gac      576
Ser Gln Ala Thr Gln Ala Pro Pro Thr Pro Ala Pro Leu Ile Arg Asp
```

```
        180                 185                 190

tca gat ctc cag tac att cta gaa ccg ccc att ccg tgg agc tct aag      624
Ser Asp Leu Gln Tyr Ile Leu Glu Pro Pro Ile Pro Trp Ser Ser Lys
        195                 200                 205

att ctt aac ctt atc ctc ctc acc cta aaa agc act aac tat tct tgc      672
Ile Leu Asn Leu Ile Leu Leu Thr Leu Lys Ser Thr Asn Tyr Ser Cys
    210                 215                 220

atg gtc tgt gtt gac cgc tcc agc cta tcc tca tgg cat gtc ctg tat      720
Met Val Cys Val Asp Arg Ser Ser Leu Ser Ser Trp His Val Leu Tyr
225                 230                 235                 240

gga ccc act caa gtc ccc agt cca ccc gac ccc caa gcc cgg tct atc      768
Gly Pro Thr Gln Val Pro Ser Pro Pro Asp Pro Gln Ala Arg Ser Ile
                245                 250                 255

ctg cga cct gcc tta gct att ccc gcc agt aat atc acc ccc ccg ttt      816
Leu Arg Pro Ala Leu Ala Ile Pro Ala Ser Asn Ile Thr Pro Pro Phe
            260                 265                 270

cct tgg acc cat tgc tat cgc cct cct ccg caa gcc atc tcc tcg gag      864
Pro Trp Thr His Cys Tyr Arg Pro Pro Pro Gln Ala Ile Ser Ser Glu
        275                 280                 285

aat tgt aac aac tct gta gtg ctg ccc ccc ttt tct ctg tct cca att      912
Asn Cys Asn Asn Ser Val Val Leu Pro Pro Phe Ser Leu Ser Pro Ile
    290                 295                 300

cct aac gtc tcc aga ccc                                             930
Pro Asn Val Ser Arg Pro
305                 310
```

<210> 12
<211> 310
<212> PRT
<213> Simian T-cell lymphotropic virus type 3

<400> 12

```
Met Gly Lys Phe Gly Leu Tyr Cys Leu Val His Leu Tyr Ile Leu Leu
1               5                   10                  15

Pro Ala Ser Ser Gly Asn Pro Ser Arg Cys Thr Leu Phe Ile Gly Ala
            20                  25                  30

Ser Ser Tyr His Ser Ser Pro Cys Gly Ser Ser Leu Pro Arg Cys Thr
        35                  40                  45

Trp Asn Leu Asp Leu Phe Ser Leu Thr Lys Asp Gln Ser Leu Ser Pro
    50                  55                  60

Pro Cys Pro Asp Leu Ile Thr Tyr Ser Gln Tyr His Lys Pro Tyr Ser
65                  70                  75                  80
```

```
Leu Tyr Val Phe Pro His Trp Ile Thr Lys Pro Asn Arg Arg Gly Leu
                85                  90                  95

Gly Tyr Tyr Ser Ala Ser Tyr Ser Asp Pro Cys Ala Ile Gln Cys Pro
            100                 105                 110

Tyr Leu Gly Cys Gln Ser Trp Thr Cys Pro Tyr Thr Gly Pro Val Ser
        115                 120                 125

Ser Pro His Trp Arg Tyr Thr Tyr Asp Leu Asn Phe Thr Gln Glu Val
    130                 135                 140

Ser Ser Val Ser Leu His Leu His Phe Ser Lys Cys Gly Ser Ser Phe
145                 150                 155                 160

Ser Phe Leu Leu Asp Ala Pro Gly Tyr Asp Pro Val Trp Phe Leu Ser
                165                 170                 175

Ser Gln Ala Thr Gln Ala Pro Pro Thr Pro Ala Pro Leu Ile Arg Asp
            180                 185                 190

Ser Asp Leu Gln Tyr Ile Leu Glu Pro Pro Ile Pro Trp Ser Ser Lys
        195                 200                 205

Ile Leu Asn Leu Ile Leu Leu Thr Leu Lys Ser Thr Asn Tyr Ser Cys
    210                 215                 220

Met Val Cys Val Asp Arg Ser Ser Leu Ser Ser Trp His Val Leu Tyr
225                 230                 235                 240

Gly Pro Thr Gln Val Pro Ser Pro Pro Asp Pro Gln Ala Arg Ser Ile
                245                 250                 255

Leu Arg Pro Ala Leu Ala Ile Pro Ala Ser Asn Ile Thr Pro Pro Phe
            260                 265                 270

Pro Trp Thr His Cys Tyr Arg Pro Pro Pro Gln Ala Ile Ser Ser Glu
        275                 280                 285

Asn Cys Asn Asn Ser Val Val Leu Pro Pro Phe Ser Leu Ser Pro Ile
    290                 295                 300

Pro Asn Val Ser Arg Pro
305                 310
```

<210> 13
<211> 153
<212> DNA
<213> Human T-cell lymphotropic virus type 1

<220>
<221> CDS
<222> (1)..(153)
<223>

<400> 13
att aaa aag cca aac cca aat ggc gga ggc tat tat tta gcc tct tat 48
Ile Lys Lys Pro Asn Pro Asn Gly Gly Gly Tyr Tyr Leu Ala Ser Tyr
1 5 10 15

tca gac cct tgt tcc tta aaa tgc cca tac ctg ggg tgc caa tca tgg 96
Ser Asp Pro Cys Ser Leu Lys Cys Pro Tyr Leu Gly Cys Gln Ser Trp
20 25 30

acc tgc ccc tat aca gga gcc gtc tcc agc ccc tac tgg aag ttt cag 144
Thr Cys Pro Tyr Thr Gly Ala Val Ser Ser Pro Tyr Trp Lys Phe Gln
35 40 45

caa gat gtc 153
Gln Asp Val
50

<210> 14
<211> 51
<212> PRT
<213> Human T-cell lymphotropic virus type 1

<400> 14

Ile Lys Lys Pro Asn Pro Asn Gly Gly Gly Tyr Tyr Leu Ala Ser Tyr
1 5 10 15

Ser Asp Pro Cys Ser Leu Lys Cys Pro Tyr Leu Gly Cys Gln Ser Trp
20 25 30

Thr Cys Pro Tyr Thr Gly Ala Val Ser Ser Pro Tyr Trp Lys Phe Gln
35 40 45

Gln Asp Val
50

<210> 15
<211> 153
<212> DNA
<213> Human T-cell lymphotropic virus type 1

<220>
<221> CDS
<222> (1)..(153)
<223>

<400> 15
gtt aaa aag cca aac cga aat ggc gga ggc tat tat tta gcc tct tat 48
Val Lys Lys Pro Asn Arg Asn Gly Gly Gly Tyr Tyr Leu Ala Ser Tyr
1 5 10 15

tca gac cct tgt tcc tta aaa tgc cca tac ctg ggg tgc caa tca tgg 96
Ser Asp Pro Cys Ser Leu Lys Cys Pro Tyr Leu Gly Cys Gln Ser Trp
20 25 30

acc tgc ccc tat aca gga gcc gtc tcc agc ccc tac tgg aag ttt cag 144
Thr Cys Pro Tyr Thr Gly Ala Val Ser Ser Pro Tyr Trp Lys Phe Gln
35 40 45

caa gat gtc 153
Gln Asp Val
50

<210> 16
<211> 51
<212> PRT
<213> Human T-cell lymphotropic virus type 1

<400> 16

Val Lys Lys Pro Asn Arg Asn Gly Gly Gly Tyr Tyr Leu Ala Ser Tyr
1 5 10 15

Ser Asp Pro Cys Ser Leu Lys Cys Pro Tyr Leu Gly Cys Gln Ser Trp
20 25 30

Thr Cys Pro Tyr Thr Gly Ala Val Ser Ser Pro Tyr Trp Lys Phe Gln
35 40 45

Gln Asp Val
50

<210> 17
<211> 153
<212> DNA
<213> Human T-cell lymphotropic virus type 1

<220>
<221> CDS
<222> (1)..(153)
<223>

<400> 17
att aaa aag cca aac cga aat ggc gga ggc tat tat tta gcc tct tat 48
Ile Lys Lys Pro Asn Arg Asn Gly Gly Gly Tyr Tyr Leu Ala Ser Tyr
1 5 10 15

tca gac cct tgt tcc tta aaa tgc cca tac ctg ggg tgc caa tca tgg 96
Ser Asp Pro Cys Ser Leu Lys Cys Pro Tyr Leu Gly Cys Gln Ser Trp
20 25 30

acc tgc ccc tat aca gga gcc gtc tcc agc ccc tac tgg aag ttt caa 144

```
Thr Cys Pro Tyr Thr Gly Ala Val Ser Ser Pro Tyr Trp Lys Phe Gln
        35                  40                  45

caa gat gtc                                                     153
Gln Asp Val
    50


<210>  18
<211>  51
<212>  PRT
<213>  Human T-cell lymphotropic virus type 1

<400>  18

Ile Lys Lys Pro Asn Arg Asn Gly Gly Gly Tyr Tyr Leu Ala Ser Tyr
1               5                   10                  15


Ser Asp Pro Cys Ser Leu Lys Cys Pro Tyr Leu Gly Cys Gln Ser Trp
            20                  25                  30


Thr Cys Pro Tyr Thr Gly Ala Val Ser Ser Pro Tyr Trp Lys Phe Gln
        35                  40                  45


Gln Asp Val
    50


<210>  19
<211>  153
<212>  DNA
<213>  Human T-cell lymphotropic virus type 1

<220>
<221>  CDS
<222>  (1)..(153)
<223>

<400>  19
att aaa aag cca aac cga aat ggc gga ggc tat tat tta gcc tct tat      48
Ile Lys Lys Pro Asn Arg Asn Gly Gly Gly Tyr Tyr Leu Ala Ser Tyr
1               5                   10                  15

tca gac cct tgt tcc tta aaa tgc cca tac ctg ggg tgc caa tca tgg      96
Ser Asp Pro Cys Ser Leu Lys Cys Pro Tyr Leu Gly Cys Gln Ser Trp
            20                  25                  30

acc tgc ccc tat aca gga ccc gtc tcc agc ccc tac tgg aag ttt cag     144
Thr Cys Pro Tyr Thr Gly Pro Val Ser Ser Pro Tyr Trp Lys Phe Gln
        35                  40                  45

caa gat gtc                                                     153
Gln Asp Val
    50


<210>  20
<211>  51
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<212> PRT
<213> Human T-cell lymphotropic virus type 1

<400> 20

Ile Lys Lys Pro Asn Arg Asn Gly Gly Gly Tyr Tyr Leu Ala Ser Tyr
1 5 10 15

Ser Asp Pro Cys Ser Leu Lys Cys Pro Tyr Leu Gly Cys Gln Ser Trp
20 25 30

Thr Cys Pro Tyr Thr Gly Pro Val Ser Ser Pro Tyr Trp Lys Phe Gln
35 40 45

Gln Asp Val
50

<210> 21
<211> 171
<212> DNA
<213> Human T-cell lymphotropic virus type 1

<220>
<221> CDS
<222> (1)..(171)
<223>

<400> 21
att aaa aag cca aac cga aat ggc gga ggc tat cat tca gcc tct tat 48
Ile Lys Lys Pro Asn Arg Asn Gly Gly Gly Tyr His Ser Ala Ser Tyr
1 5 10 15

tca gac cct tgt tcc tta aag tgc cca tac ctg ggg tgc caa tca tgg 96
Ser Asp Pro Cys Ser Leu Lys Cys Pro Tyr Leu Gly Cys Gln Ser Trp
20 25 30

acc tgc ccc tat gca gga gcc gtc tcc agc ccc tac tgg aag ttt cag 144
Thr Cys Pro Tyr Ala Gly Ala Val Ser Ser Pro Tyr Trp Lys Phe Gln
35 40 45

caa gat gtc aat ttt acc cag gaa gta 171
Gln Asp Val Asn Phe Thr Gln Glu Val
50 55

<210> 22
<211> 57
<212> PRT
<213> Human T-cell lymphotropic virus type 1

<400> 22

Ile Lys Lys Pro Asn Arg Asn Gly Gly Gly Tyr His Ser Ala Ser Tyr
1 5 10 15

Ser Asp Pro Cys Ser Leu Lys Cys Pro Tyr Leu Gly Cys Gln Ser Trp

20 25 30

Thr Cys Pro Tyr Ala Gly Ala Val Ser Ser Pro Tyr Trp Lys Phe Gln
35 40 45

Gln Asp Val Asn Phe Thr Gln Glu Val
50 55

<210> 23
<211> 153
<212> DNA
<213> Human T-cell lymphotropic virus type 2

<220>
<221> CDS
<222> (1)..(153)
<223>

<400> 23
ata aga aag cca aac aga cag ggc cta ggg tac tac tcg cct tcc tac 48
Ile Arg Lys Pro Asn Arg Gln Gly Leu Gly Tyr Tyr Ser Pro Ser Tyr
1 5 10 15

aat gac cct tgc tcg cta caa tgc ccc tac ttg ggc tcc caa tca tgg 96
Asn Asp Pro Cys Ser Leu Gln Cys Pro Tyr Leu Gly Ser Gln Ser Trp
20 25 30

aca tgc cca tac acg gcc ccc gtc tcc act cca tcc tgg aat ttt cat 144
Thr Cys Pro Tyr Thr Ala Pro Val Ser Thr Pro Ser Trp Asn Phe His
35 40 45

tca gat gta 153
Ser Asp Val
50

<210> 24
<211> 51
<212> PRT
<213> Human T-cell lymphotropic virus type 2

<400> 24

Ile Arg Lys Pro Asn Arg Gln Gly Leu Gly Tyr Tyr Ser Pro Ser Tyr
1 5 10 15

Asn Asp Pro Cys Ser Leu Gln Cys Pro Tyr Leu Gly Ser Gln Ser Trp
20 25 30

Thr Cys Pro Tyr Thr Ala Pro Val Ser Thr Pro Ser Trp Asn Phe His
35 40 45

Ser Asp Val
50

<210> 25
<211> 11
<212> PRT
<213> Homo sapiens

<400> 25

Asn Ala Pro Gln Lys Val Ile Glu Glu Phe Tyr
1 5 10

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Gln Tyr Val Glu Gln Leu Cys
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